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**UNITED STATES DISTRICT COURT**
**DISTRICT OF NEW JERSEY**

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|---|---|
| **CORCEPT THERAPEUTICS, INC.,**<br><br>**Plaintiff,**<br><br>**v.**<br><br>**SUN PHARMA GLOBAL FZE, SUN PHARMA GLOBAL INC., SUN PHARMACEUTICAL INDUSTRIES, INC., and SUN PHARMACEUTICAL INDUSTRIES LIMITED,**<br><br>**Defendants.** | **Civil Action No. 19-15678 (SDW)(CLW)**<br><br>**(Filed Electronically)** |

**FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT**[1]

Plaintiff Corcept Therapeutics, Inc. ("Corcept"), by its undersigned attorneys, for its Complaint against defendants Sun Pharma Global FZE ("Sun FZE"), Sun Pharma Global Inc. ("Sun Pharma"), Sun Pharmaceutical Industries, Inc. ("Sun Inc."), and Sun Pharmaceutical Industries Limited ("Sun Ltd.") (collectively, "Sun"), alleges as follows:

[1] Plaintiff Corcept Therapeutics, Inc. files this First Amended Complaint with consent from Defendants Sun Pharma Global FZE, Sun Pharma Global Inc., Sun Pharmaceutical Industries, Inc., and Sun Pharmaceutical Industries Limited pursuant to Fed. R. Civ. P. 15(a)(2).

## Nature of the Action

1. This complaint is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from Sun's filing of an Abbreviated New Drug Application ("ANDA") No. 213387 ("Sun's ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of Corcept's 300 mg mifepristone drug product ("Sun's Proposed Product") prior to the expiration of United States Patent Nos. 8,921,348 ("the '348 Patent"),10,195,214 ("the '214 Patent"), 9,829,495 ("the '495 Patent"), and 10,500,216 ("the '216 patent") (together, "the patents-in-suit"), owned by Corcept.

## The Parties

2. Plaintiff Corcept is a biopharmaceutical company committed to improving the lives of patients worldwide. Corcept focuses on, and heavily invests in, the discovery and development of drugs that regulate the effects of cortisol for the treatment of severe and life-threatening conditions, including Cushing's syndrome. Corcept is an industry leader for the development of orphan-status rare disease drugs, including KORLYM®. Corcept is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 149 Commonwealth Dr., Menlo Park, CA 94025.

3. On information and belief, defendant Sun FZE is a corporation organized and existing under the laws of the United Arab Emirates, having a principal place of business at Office # 43, Block Y, SAIF-Zone, P.O. Box #122304, Sharjah, United Arab Emirates. On information and belief, Sun FZE is a wholly-owned subsidiary of Sun Ltd.

4. On information and belief, defendant Sun Pharma is a corporation organized and existing under the laws of the British Virgin Islands, and maintains a post office box at

International Trust Building, P.O. Box No. 659, Road Town, Tortola, British Virgin Islands. On information and belief, Sun Pharma is a wholly-owned subsidiary of Sun Ltd.

5. On information and belief, defendant Sun Inc. is a corporation organized and existing under the laws of the State of Michigan, having a principal place of business at 1 Commerce Drive, Cranbury, New Jersey 08512. On information and belief, Sun Inc. is a wholly-owned subsidiary of Sun Ltd.

6. On information and belief, defendant Sun Ltd. is a corporation organized and existing under the laws of existing under the laws of India, having a principal place of business at Sun House, CTS No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai 400 063, Maharashtra, India.

**The Patents-in-Suit**

7. On December 30, 2014, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '348 Patent, entitled "Optimizing Mifepristone Levels in Plasma Serum of Patients Suffering from Mental Disorders Treatable with Glucocorticoid Receptor Antagonists" to Corcept as assignee of the inventor Joseph K. Belanoff. A copy of the '348 Patent is attached hereto as Exhibit A.

8. On February 5, 2019, the USPTO duly and lawfully issued the '214 Patent, entitled, "Concomitant Administration of Glucocorticoid Receptor Modulators and CYP3A Inhibitors" to Corcept as assignee of the inventor Joseph K. Belanoff. A copy of the '214 Patent is attached hereto as Exhibit B.

9. On November 28, 2017, the USPTO duly and lawfully issued the '495 Patent, entitled, "Method for Differentially Diagnosing ACTH-Dependent Cushing's Syndrome" to Corcept as assignee of the inventor Andreas G. Moraitis. A copy of the '495 Patent is attached hereto as Exhibit C.

10. On December 10, 2019, the USPTO duly and lawfully issued the '216 Patent, entitled, "Optimizing Mifepristone Absorption" to Corcept as assignee of the inventors Joe Belanoff, Robert Roe, and Caroline Loewy. A copy of the '216 Patent is attached hereto as Exhibit D.

**The KORLYM® Drug Product**

11. Corcept holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for mifepristone tablets (NDA No. 202107), which it sells under the trade name KORLYM®. KORLYM® is an FDA-approved medication for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery. The claims of the patents-in-suit cover, inter alia, methods of use and administration of mifepristone.

12. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Product with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to KORLYM®.

**Jurisdiction and Venue**

13. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

14. The Court has personal jurisdiction over Sun by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

15. On information and belief, Sun FZE, Sun Pharma, Sun Inc., and Sun Ltd. develop, manufacture, distribute, market, offer to sell, and sell generic drug products for sale and use throughout the United States, including within this Judicial District.

16. On information and belief, Sun FZE, Sun Pharma, Sun Inc., and Sun Ltd. prepare and/or aid in the submission of ANDAs to the FDA.

17. On information and belief, Sun FZE, Sun Pharma, Sun Inc., and Sun Ltd. derive substantial revenue from selling generic products throughout the United States, including in this Judicial District.

18. This Court has personal jurisdiction over Sun because, *inter alia*, it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2), and, on information and belief, Sun intends a future course of conduct that includes acts of patent infringement in New Jersey.

19. On information and belief, Sun FZE, Sun Pharma, Sun Inc., and Sun Ltd. actively participated in the submission of Sun's ANDA. On information and belief, Sun Ltd. will work in concert with Sun FZE, Sun Pharma, Sun Inc., and/or other subsidiaries towards the regulatory approval, manufacturing, use, importation, marketing, offer for sale, sale, and distribution of generic pharmaceutical products, including Sun's Proposed Product, throughout the United States, including in New Jersey and in this Judicial District, prior to the expiration of the patents-in-suit.

20. On information and belief, Sun seeks approval from the FDA to sell Sun's Proposed Product throughout the United States, including in this Judicial District. On information and belief, this Judicial District will be a destination for the generic drug product described in Sun's ANDA.

21. This Court has personal jurisdiction over Sun because Sun has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Sun regularly and

continuously transacts business within New Jersey, directly or indirectly, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. For example, Sun's website states its "US headquarters are in Cranbury, New Jersey," it has "distribution and customer service teams at multiple locations across the country," and "Sun Pharma's latest acquisition of a majority interest in Ranbaxy Laboratories Limited (Ranbaxy) and its Ohm Laboratories facilities in . . . New Jersey makes it the largest Indian pharma company in the US market." Sun Pharma USA, http://www.sunpharma.com/usa (last visited June 28, 2019).

22. This Court has personal jurisdiction over Sun FZE by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Sun FZE purposefully has conducted and continues to conduct business in this Judicial District.

23. On information and belief, Sun FZE is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

24. On information and belief, Sun FZE, alone or through Sun Pharma, Sun Inc., and/or Sun Ltd., or through distributors, retailers, and/or wholesalers, manufactures and/or distributes generic drugs for sale and use throughout the United States, including in this Judicial District.

25. On information and belief, Sun FZE has previously consented to this Court's jurisdiction and has availed itself of the protections afforded by the Court by asserting counterclaims against plaintiffs in this Judicial District. *See, e.g., Novartis Pharmaceuticals Corp., et al. v. Sun Pharma Global FZE, et al.*, Civil Action No. 12-4393 (SDW)(MCA); *The Medicines Co. v. Sun Pharma Global FZE, et al.*, Civil Action No. 11-6819 (PGS)(DEA).

26. In the alternative, this Court has personal jurisdiction over Sun FZE because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Corcept's claims arise under federal law; (b) Sun FZE is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Sun FZE has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Sun FZE satisfies due process.

27. This Court has personal jurisdiction over Sun Pharma by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Sun Pharma purposefully has conducted and continues to conduct business in this Judicial District.

28. On information and belief, Sun Pharma is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

29. On information and belief, Sun Pharma, alone or through Sun FZE, Sun Inc., and/or Sun Ltd., or through distributors, retailers, and/or wholesalers, manufactures and/or distributes generic drugs for sale and use throughout the United States, including in this Judicial District.

30. On information and belief, Sun Pharma has previously consented to this Court's jurisdiction and has availed itself of the protections afforded by the Court by asserting counterclaims against plaintiffs in this Judicial District. *See, e.g., Otsuka Pharm. Co. v. Sun Pharm. Indus. Ltd., et al.*, Civil Action No. 14-4307 (JBS)(KMW); *Otsuka Pharm. Co. v. Sun*

*Pharm. Indus. Ltd., et al.*, Civil Action No. 14-6397 (JBS) (KMW); *Aventis Pharms. Inc., et al. v. Sun Pharma Global Inc., et al.*, Civil Action No. 09-325 (GEB)(MCA).

31. In the alternative, this Court has personal jurisdiction over Sun Pharma because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Corcept's claims arise under federal law; (b) Sun Pharma is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Sun Pharma has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Sun Pharma satisfies due process.

32. This Court has personal jurisdiction over Sun Inc. by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Sun Inc. purposefully has conducted and continues to conduct business in this Judicial District.

33. On information and belief, Sun Inc. is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

34. On information and belief, Sun Inc., alone or through Sun FZE, Sun Pharma, and/or Sun Ltd., or through distributors, retailers, and/or wholesalers, manufactures and/or distributes generic drugs for sale and use throughout the United States, including in this Judicial District.

35. On information and belief, Sun, through at least Sun Inc., maintains physical places of business in at least Princeton, New Jersey and Cranbury, New Jersey.

36. On information and belief, Sun Inc. is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID Nos. 0100954087 and/or 0100970132 and is registered as manufacturer and wholesaler with the New Jersey Department of Health under Registration No. 5003437.

37. On information and belief, Sun Inc. has previously consented to this Court's jurisdiction and has availed itself of the protections afforded by the Court by asserting counterclaims against plaintiffs in this Judicial District. *See, e.g.*, *Janssen Pharms. Inc. v Sun Pharma Global FZE, et al.*, Civil Action No. 11-6089 (SRC)(CLW); *Otsuka Pharm. Co. v. Sun Pharm. Indus. Ltd., et al.*, Civil Action No. 14-4307 (JBS)(KMW); *Otsuka Pharm. Co. v. Sun Pharm. Indus. Ltd.*, Civil Action No. 14-6397 (JBS)(KMW).

38. On information and belief, Sun FZE, Sun Global, and Sun Inc. act for the benefit of and at the direction of Sun Ltd., and are agents and/or alter egos of Sun Ltd.

39. This Court has personal jurisdiction over Sun Ltd. by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey. On information and belief, Sun Ltd. purposefully has conducted and continues to conduct business in this Judicial District.

40. On information and belief, Sun Ltd. is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

41. On information and belief, Sun Ltd., alone or through Sun FZE, Sun Pharma, and/or Sun Inc., or through distributors, retailers, and/or wholesalers, manufactures and/or distributes generic drugs for sale and use throughout the United States, including in this Judicial District.

42. This Court also has personal jurisdiction over Sun Ltd. because Sun Ltd. has purposefully availed itself of the rights and benefits of New Jersey law by engaging in systematic and continuous contacts with the State of New Jersey. On information and belief, Sun Ltd. regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey.

43. This Court has personal jurisdiction over Sun Ltd. because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its subsidiary, agent, and/or alter ego, Sun Inc., a company registered as manufacturer and wholesaler with the New Jersey Department of Health under Registration No. 5003437 and registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID Nos. 0100954087 and/or 0100970132; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey, including through, directly or indirectly, Sun Inc. On information and belief, Sun Inc. acts at the direction, and for the benefit, of Sun Ltd., and is controlled and/or dominated by Sun Ltd.

44. On information and belief, Sun Ltd. has previously invoked, stipulated, and/or consented to personal jurisdiction in this Judicial District in numerous prior patent cases.

45. Sun Ltd. has previously been sued in this Judicial District and has availed itself of New Jersey courts through the assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g., Jazz Pharmaceuticals, Inc., et al. v. Sun Pharmaceutical Industries Ltd., et al.*, Civil Action No. 15-8229 (ES)(JAD); *Boehringer Ingelheim Pharmaceuticals Inc., et al. v. Sun Pharmaceutical Industries Ltd., et al.*, Civil Action

No. 15-5982 (PGS)(TJB); *Jazz Pharmaceuticals, Inc. v. Sun Pharmaceutical Industries Ltd., et al.*, Civil Action No. 15-3217 (ES)(JAD); *Otsuka Pharmaceutical Co., Ltd. v. Sun Pharmaceutical Industries Ltd., et al.*, Civil Action No. 14-6397 (JBS)(KMW); *Otsuka Pharmaceutical Co., Ltd. v. Sun Pharmaceutical Industries, Inc., et al.*, Civil Action No. 14-4307 (JBS)(KMW); *Cephalon, Inc. v. Sun Pharmaceutical Industries, Inc., et al.*, Civil Action No. 11-5474 (FLW)(DEA); *Depomed, Inc., et al. v. Sun Pharmaceutical Industries, Inc., et al.*, Civil Action No. 11-3553 (JAP)(TJB).

46. Sun Ltd. has further availed itself of the jurisdiction of this Court by initiating litigation in this Judicial District. *See, e.g., Sun Pharmaceutical Industries Ltd., et al. v. Altana Pharma AG, et al.*, Civil Action No. 05-2391.

47. In the alternative, this Court has personal jurisdiction over Sun Ltd. because the requirements of Federal Rule of Civil Procedure 4(k)(2) are met as (a) Corcept's claims arise under federal law; (b) Sun Ltd. is a foreign defendant not subject to general personal jurisdiction in the courts of any state; and (c) Sun Ltd. has sufficient contacts with the United States as a whole, including, but not limited to, preparing and submitting ANDAs to the FDA and/or manufacturing, importing, offering to sell, and/or selling pharmaceutical products that are distributed throughout the United States, such that this Court's exercise of jurisdiction over Sun Ltd. satisfies due process.

48. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

**Acts Giving Rise To This Suit**

49. Pursuant to Section 505 of the FFDCA, Sun filed ANDA No. 213387 seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation of Sun's Proposed Product, before the patents-in-suit expire.

50. No earlier than June 07, 2019, Sun sent written notice of a Paragraph IV Certification ("Sun's Notice Letter") to Corcept. According to Sun's Notice Letter, Sun filed an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Sun's Proposed Product before expiration of the patents listed in the Orange Book with respect to KORLYM®.

51. Sun's Notice Letter alleges that the claims of the patents-in-suit are invalid and/or will not be infringed by the activities described in Sun's ANDA.

52. On information and belief, in connection with the filing of its ANDA as described above, Sun provided a written certification to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Sun's Paragraph IV Certification"), alleging that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Sun's ANDA.

53. On information and belief, following FDA approval of Sun's ANDA, Sun FZE, Sun Pharma, Sun Inc., and Sun Ltd. will work in concert with one another to make, use, offer to sell, or sell Sun's Proposed Product throughout the United States, or import such generic products into the United States.

**Count I: Infringement of the '348 Patent**

54. Corcept repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

55. Sun's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Sun's Proposed Product, prior to the expiration of the '348 Patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

56. A justiciable controversy exists between the parties hereto as to the infringement of the ’348 Patent.

57. Unless enjoined by this Court, upon FDA approval of Sun’s ANDA, Sun will infringe one or more claims of the ’348 Patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Sun’s Proposed Product in the United States.

58. Unless enjoined by this Court, upon FDA approval of Sun’s ANDA, Sun will induce infringement of one or more claims of the ’348 Patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Sun’s Proposed Product in the United States. On information and belief, upon FDA approval of Sun’s ANDA, Sun will intentionally encourage acts of direct infringement with knowledge of the ’348 Patent and knowledge that its acts are encouraging infringement.

59. Unless enjoined by this Court, upon FDA approval of Sun’s ANDA, Sun will contributorily infringe one or more claims of the ’348 Patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Sun’s Proposed Product in the United States. On information and belief, Sun knew and knows that Sun’s Proposed Product is designed for a use that infringes one or more claims of the ’348 Patent, and Sun’s Proposed Product lacks a substantial non-infringing use.

60. Failure to enjoin Sun’s infringement of the ’348 Patent will substantially and irreparably damage Corcept.

61. Corcept does not have an adequate remedy at law.

**Count II: Infringement of the ’214 Patent**

62. Corcept repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

63. Sun's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Sun's Proposed Product, prior to the expiration of the '214 Patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

64. A justiciable controversy exists between the parties hereto as to the infringement of the '214 Patent.

65. Unless enjoined by this Court, upon FDA approval of Sun's ANDA, Sun will infringe one or more claims of the '214 Patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Sun's Proposed Product in the United States.

66. Unless enjoined by this Court, upon FDA approval of Sun's ANDA, Sun will induce infringement of one or more claims of the '214 Patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Sun's Proposed Product in the United States. On information and belief, upon FDA approval of Sun's ANDA, Sun will intentionally encourage acts of direct infringement with knowledge of the '214 Patent and knowledge that its acts are encouraging infringement.

67. Unless enjoined by this Court, upon FDA approval of Sun's ANDA, Sun will contributorily infringe one or more claims of the '214 Patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Sun's Proposed Product in the United States. On information and belief, Sun knew and knows that Sun's Proposed Product is designed for a use that infringes one or more claims of the '214 Patent, and Sun's Proposed Product lacks a substantial non-infringing use.

68. Failure to enjoin Sun's infringement of the '214 Patent will substantially and irreparably damage Corcept.

69. Corcept does not have an adequate remedy at law.

**Count III: Infringement of the '495 Patent**

70. Corcept repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

71. Sun's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Sun's Proposed Product, prior to the expiration of the '495 Patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

72. A justiciable controversy exists between the parties hereto as to the infringement of the '495 Patent.

73. Unless enjoined by this Court, upon FDA approval of Sun's ANDA, Sun will infringe one or more claims of the '495 Patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Sun's Proposed Product in the United States.

74. Unless enjoined by this Court, upon FDA approval of Sun's ANDA, Sun will induce infringement of one or more claims of the '495 Patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Sun's Proposed Product in the United States. On information and belief, upon FDA approval of Sun's ANDA, Sun will intentionally encourage acts of direct infringement with knowledge of the '495 Patent and knowledge that its acts are encouraging infringement.

75. Unless enjoined by this Court, upon FDA approval of Sun's ANDA, Sun will contributorily infringe one or more claims of the '495 Patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Sun's Proposed Product in the United States. On information and belief, Sun knew and knows that Sun's Proposed Product is designed

for a use that infringes one or more claims of the ’495 Patent, and Sun’s Proposed Product lacks a substantial non-infringing use.

76. Failure to enjoin Sun’s infringement of the ’495 Patent will substantially and irreparably damage Corcept.

77. Corcept does not have an adequate remedy at law.

**Count IV: Infringement of the ’216 Patent**

78. Corcept repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

79. Sun’s submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Sun’s Proposed Product, prior to the expiration of the ’216 Patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

80. A justiciable controversy exists between the parties hereto as to the infringement of the ’216 Patent.

81. Unless enjoined by this Court, upon FDA approval of Sun’s ANDA, Sun will infringe one or more claims of the ’216 Patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Sun’s Proposed Product in the United States.

82. Unless enjoined by this Court, upon FDA approval of Sun’s ANDA, Sun will induce infringement of one or more claims of the ’216 Patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Sun’s Proposed Product in the United States. On information and belief, upon FDA approval of Sun’s ANDA, Sun will intentionally encourage acts of direct infringement with knowledge of the ’216 Patent and knowledge that its acts are encouraging infringement.

83. Unless enjoined by this Court, upon FDA approval of Sun's ANDA, Sun will contributorily infringe one or more claims of the '216 Patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Sun's Proposed Product in the United States. On information and belief, Sun knew and knows that Sun's Proposed Product is designed for a use that infringes one or more claims of the '216 Patent, and Sun's Proposed Product lacks a substantial non-infringing use.

84. Failure to enjoin Sun's infringement of the '216 Patent will substantially and irreparably damage Corcept.

85. Corcept does not have an adequate remedy at law.

**PRAYER FOR RELIEF**

86. WHEREFORE, Plaintiff Corcept respectfully requests the following relief:

(A) A Judgment that Sun infringed the patents-in-suit by submitting ANDA No. 213387;

(B) A Judgment that Sun has infringed, and that Sun's making, using, offering to sell, selling, or importing Sun's Proposed Product will infringe one or more claims of the patents-in-suit;

(C) An Order that the effective date of FDA approval of ANDA No. 213387 be a date no earlier than the later of the expiration of each patent-in-suit, or any later expiration of exclusivity to which Corcept is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Sun and its officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Sun's Proposed Product until after the expiration of the each patent-in-suit, or any later expiration of exclusivity to which Corcept is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Sun, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from practicing any method claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of each patent-in-suit, or any later expiration of exclusivity to which Corcept is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Sun's Proposed Product will directly infringe, induce and/or contribute to infringement of the patents-in-suit;

(G) To the extent that Sun has committed any acts with respect the methods claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Corcept damages for such acts;

(H) If Sun engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Sun's Proposed Product prior to the expiration of the patents-in-suit, a Judgment awarding damages to Corcept resulting from such infringement, together with interest;

(I) A Judgment declaring that the patent-in-suit remains valid and enforceable;

(J) A Judgment awarding Corcept its costs and expenses incurred in this action; and

(K) Such further and other relief as this Court may deem just and proper.

Dated: January 23, 2020

By: s/ William C. Baton

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# EXHIBIT A

US008921348B2

(12) **United States Patent**
**Belanoff**

(10) **Patent No.: US 8,921,348 B2**
(45) **Date of Patent: Dec. 30, 2014**

(54) **OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS**

(71) Applicant: **Corcept Therapeutics**, Menlo Park, CA (US)

(72) Inventor: **Joseph K. Belanoff**, Woodside, CA (US)

(73) Assignee: **Corcept Therapeutics, Inc.**, Menlo Park, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/065,792**

(22) Filed: **Oct. 29, 2013**

(65) **Prior Publication Data**

US 2014/0162993 A1 Jun. 12, 2014

**Related U.S. Application Data**

(63) Continuation of application No. 12/199,114, filed on Aug. 27, 2008, now Pat. No. 8,598,149.

(60) Provisional application No. 60/969,027, filed on Aug. 30, 2007.

(51) **Int. Cl.**

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|---|---|
| ***A61K 31/56*** | (2006.01) |
| ***G01N 33/49*** | (2006.01) |
| ***A61K 31/575*** | (2006.01) |

(52) **U.S. Cl.**
CPC ..... ***G01N 33/49*** (2013.01); ***A61K 31/56*** (2013.01); ***A61K 31/575*** (2013.01)
USPC ..... **514/178**

(58) **Field of Classification Search**
USPC ..... 514/178
See application file for complete search history.

(56) **References Cited**

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(57) **ABSTRACT**

The present invention provides a method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone. The method comprises the steps of treating the patient with seven or more daily doses of mifepristone over a period of seven or more days; testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

**7 Claims, 6 Drawing Sheets**

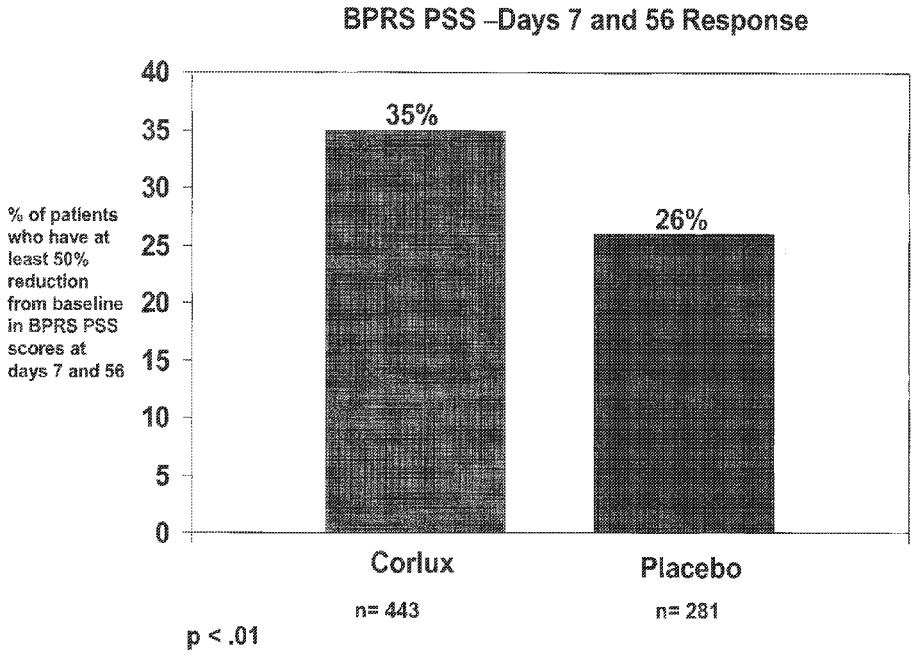


Figure 1.

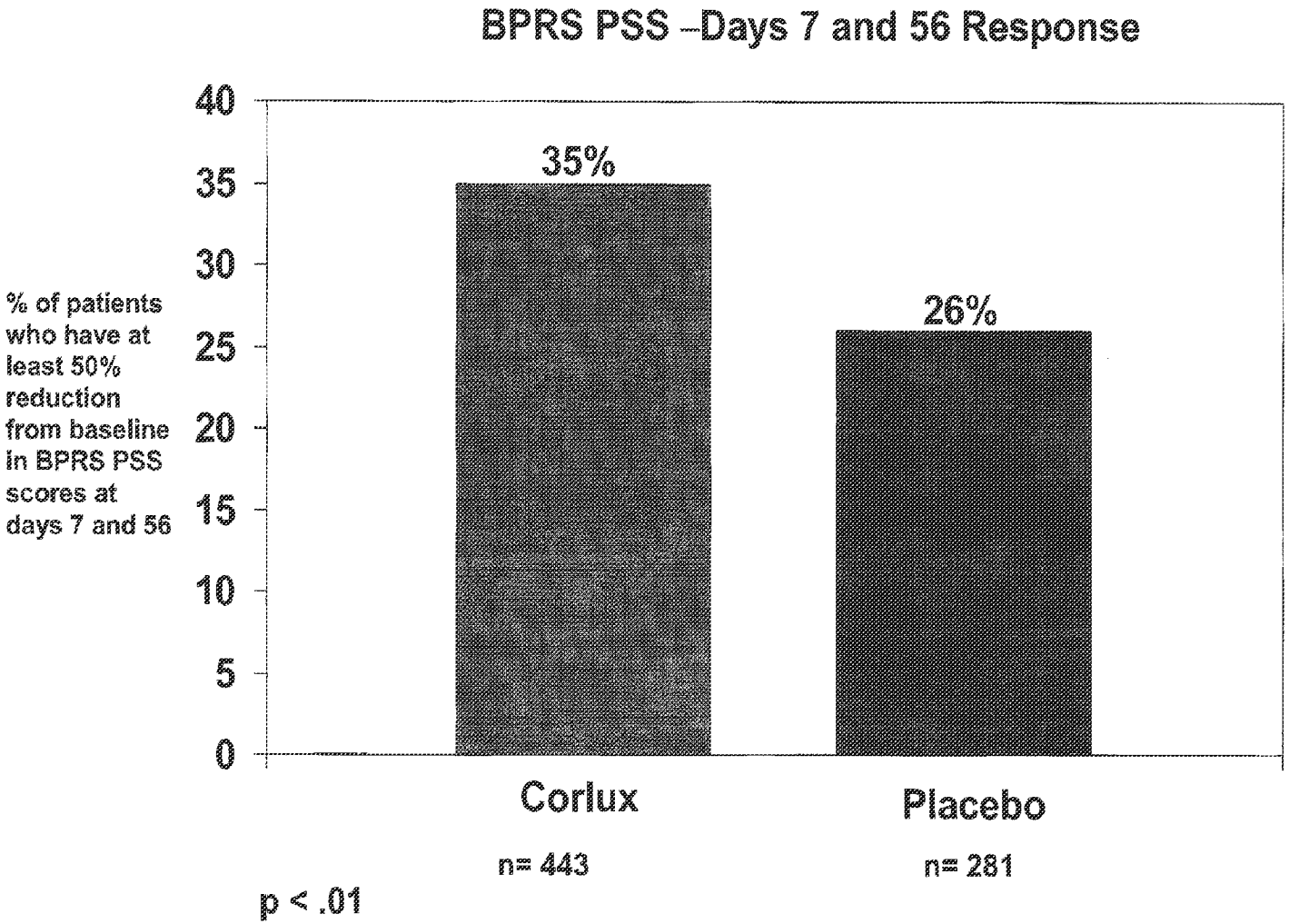

BPRS PSS –Days 7 and 56 Response
% of patients who have at least 50% reduction from baseline in BPRS PSS scores at days 7 and 56
40
35
30
25
20
15
10
5
0
35%
26%
Corlux
Placebo
n= 443
n= 281
p < .01

Figure 2.

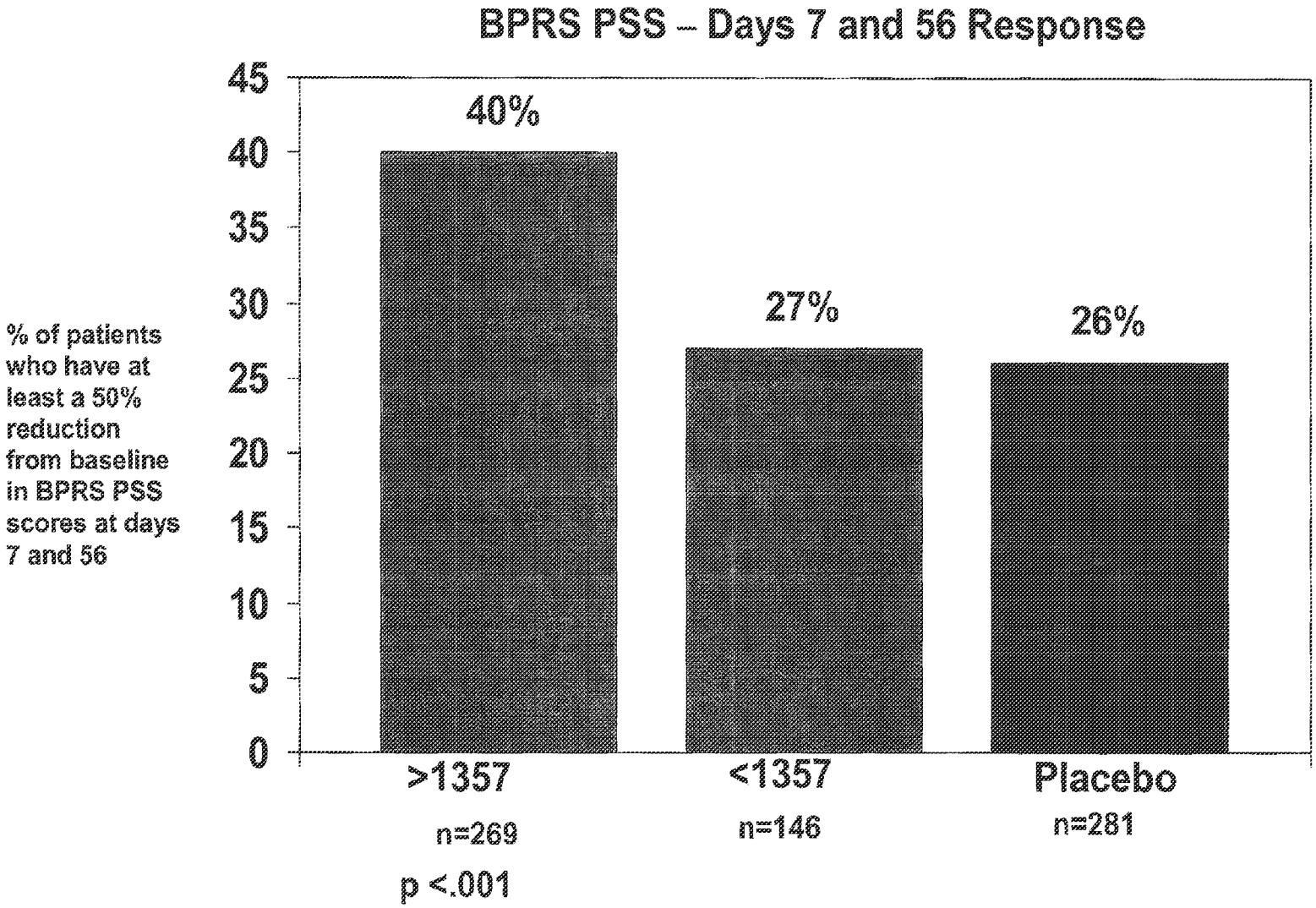

BPRS PSS – Days 7 and 56 Response
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
45
40
35
30
25
20
15
10
5
0
40%
27%
26%
>1357
n=269
<1357
n=146
Placebo
n=281
p <.001

Figure 3.

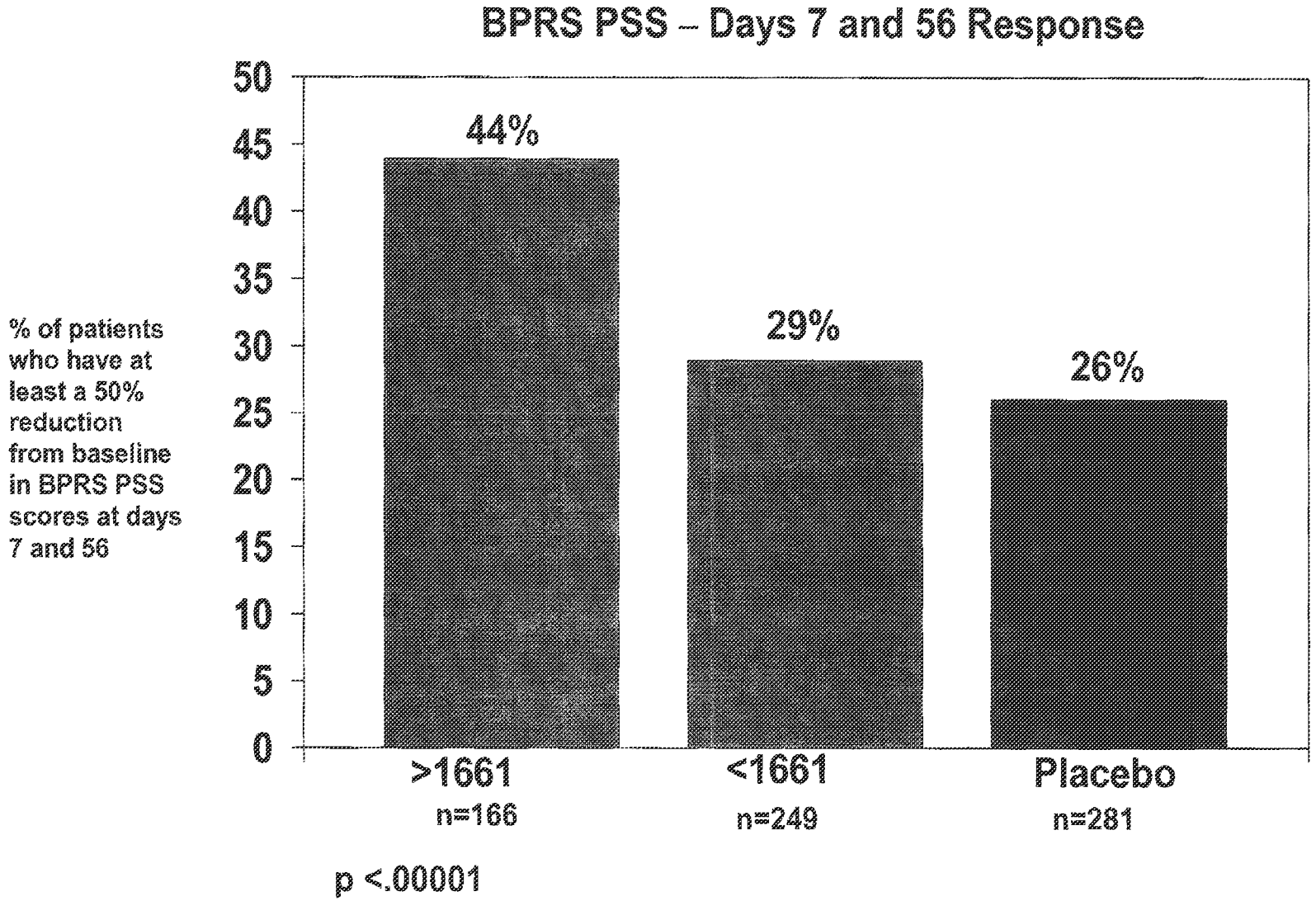

BPRS PSS – Days 7 and 56 Response
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
50
45
40
35
30
25
20
15
10
5
0
44%
29%
26%
>1661
n=166
<1661
n=249
Placebo
n=281
p <.00001

Figure 4.

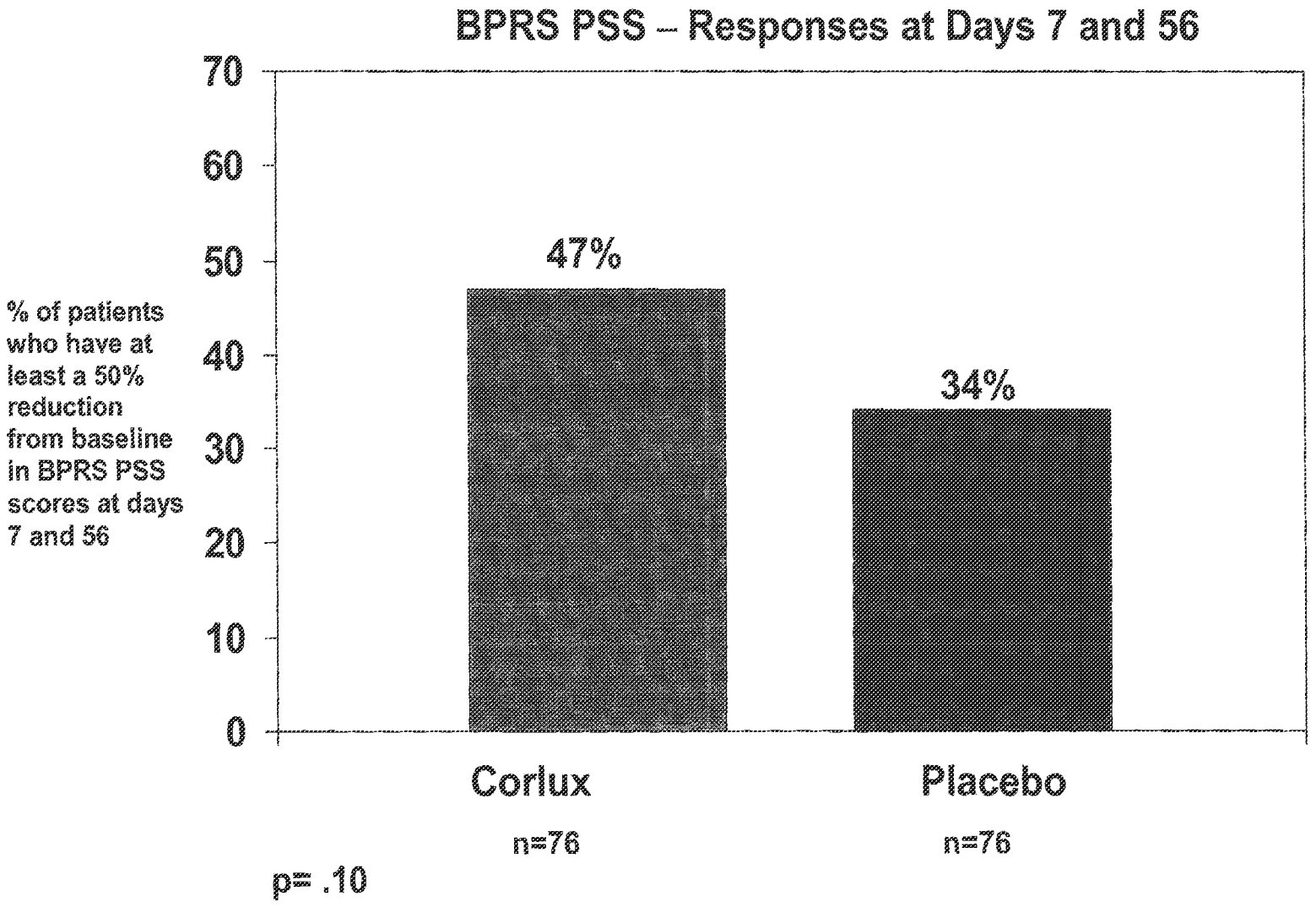

BPRS PSS – Responses at Days 7 and 56
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
70
60
50
40
30
20
10
0
47%
34%
Corlux
n=76
Placebo
n=76
p= .10

Figure 5.

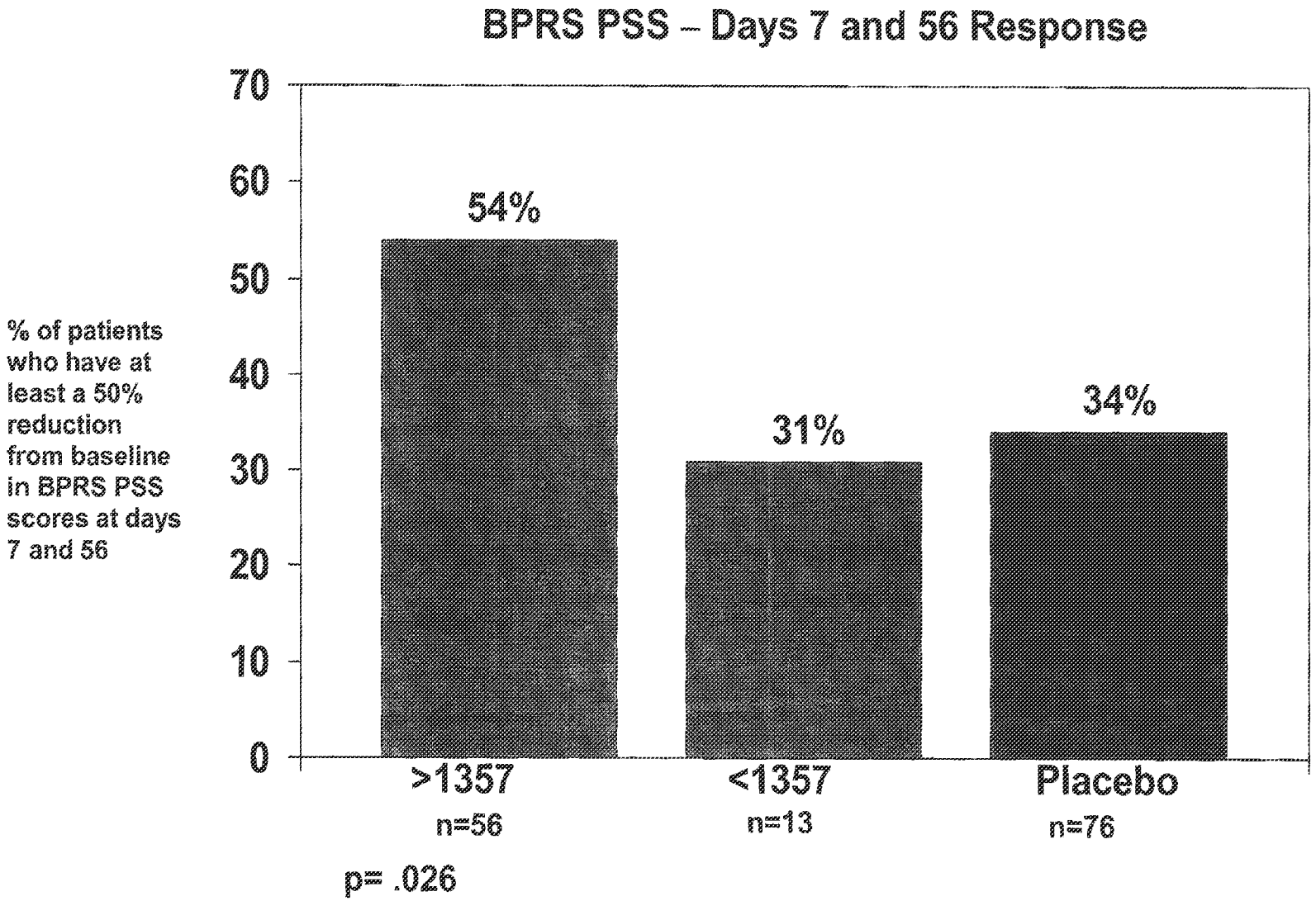
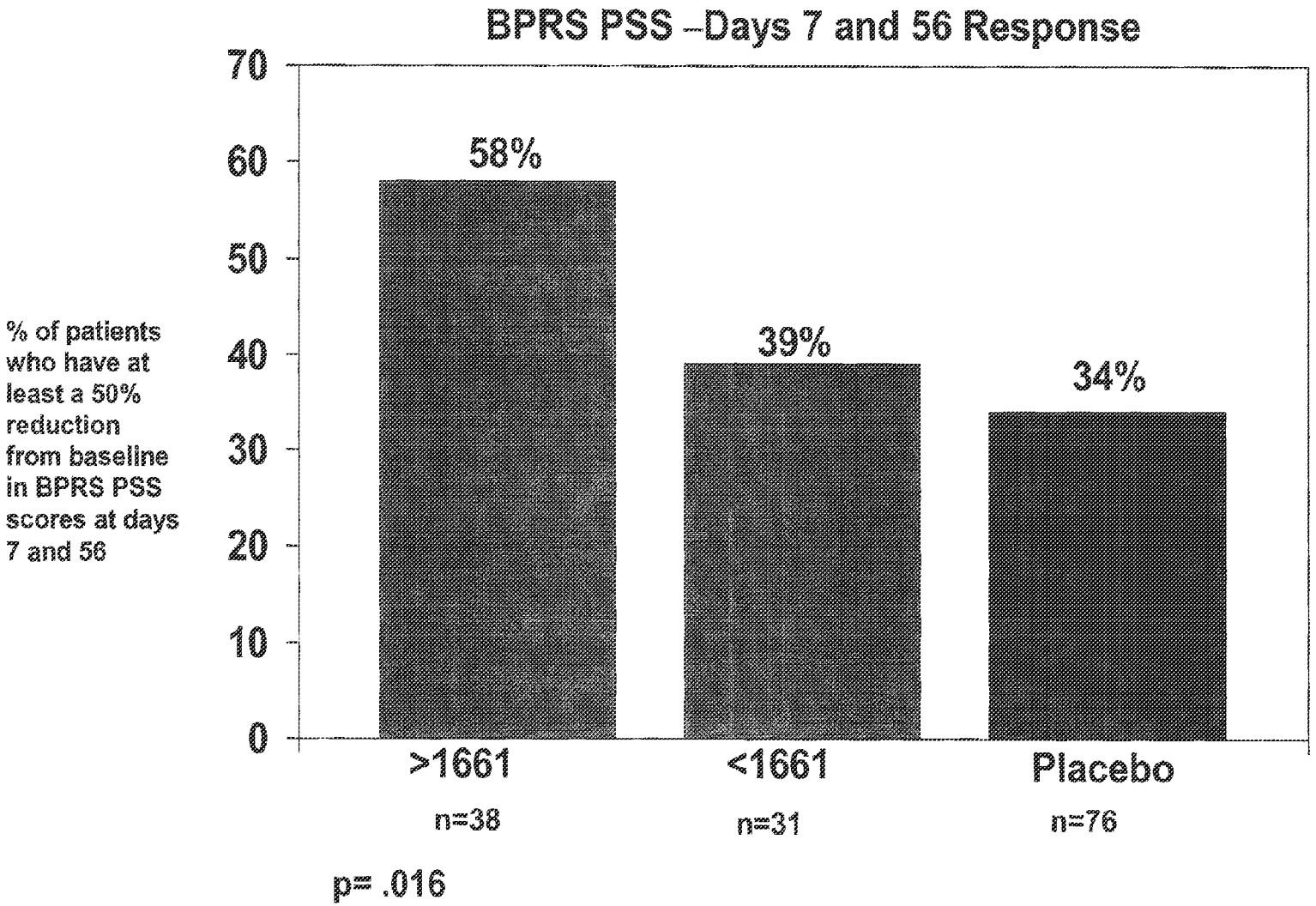

BPRS PSS – Days 7 and 56 Response
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
70
60
50
40
30
20
10
0
54%
31%
34%
>1357
n=56
<1357
n=13
Placebo
n=76
p= .026

Figure 6.


BPRS PSS --Days 7 and 56 Response
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
70
60
50
40
30
20
10
0
58%
39%
34%
>1661
<1661
Placebo
n=38
n=31
n=76
p= .016

# OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

## CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/969,027, filed Aug. 30, 2007, the disclosure of which is incorporated herein in its entirety.

## STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

Not Applicable

## REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

Not Applicable

## BACKGROUND OF THE INVENTION

It has been surprisingly discovered that administration of the same dose of mifepristone can produce widely varying blood serum levels in different patients. The varied blood serum levels can result in some patients not receiving an efficacious dose of mifepristone. For the same dose of mifepristone, the blood serum levels can differ by as much as 800% from one patient to another. Thus, a method for ensuring that the blood serum levels of mifepristone remain in an efficacious and safe range is needed.

## BRIEF SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone, the method comprising: treating the patient with seven or more daily doses of mifepristone over a period of seven or more days; testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

In some embodiments, the mental disorder is a member selected from the group consisting of a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression. In other embodiments, the stress disorder is a member selected from the group consisting of Acute Stress Disorder, Post-Traumatic Stress Disorder and Brief Psychotic Disorder with Marked Stressor(s).

In another embodiment, each of the seven or more daily doses of mifepristone are administered orally. In other embodiments, the patient is treated with 28 or more daily doses over a period of 28 or more days.

In a further embodiment, the testing is performed by a plasma sampling collection device suitable for detecting mifepristone serum levels.

In other embodiments, the adjusting step comprises increasing the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.



In a second embodiment, the present invention provides a kit for treating a mental disorder amenable to treatment by mifepristone, the kit comprising: seven daily doses of mifepristone; and a plasma sampling collection device suitable for detecting mifepristone serum levels.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a comparison of patients receiving Corlux vs. placebo on primary endpoint (OC) for all studies. Of the patients receiving Corlux, 35% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 26% of patients receiving the placebo.

FIG. **2** shows a comparison of patients with plasma levels >1357 ng/mL vs. <1357 ng/mL vs. placebo (OC) for all studies. Of the patients having plasma levels of greater than 1357 ng/mL, 40% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 27% of patients having plasma levels of less than 1357 ng/mL and 26% of patients receiving the placebo.

FIG. **3** shows a comparison of patients with plasma levels >1661 ng/ml vs. placebo (OC) for all studies. Of the patients having plasma levels of greater than 1661 ng/mL, 44% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 29% of patients having plasma levels of less than 1661 ng/mL and 26% of patients receiving the placebo.

FIG. **4** shows a comparison of patients receiving Corlux vs. placebo on primary endpoint (OC) for the 1200 mg group. Of the patients receiving the 1200 mg dose of Corlux, 47% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 34% of patients receiving the placebo.

FIG. **5** shows a comparison of patients with plasma levels >1357 ng/ml vs. placebo (OC) for the 1200 mg group. Of the patients in the 1200 mg group having plasma levels of greater than 1357 ng/mL, 54% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 31% of patients having plasma levels of less than 1357 ng/mL and 34% of patients receiving the placebo.

FIG. **6** shows a comparison of patients with plasma levels >1661 ng/ml vs. placebo (OC) for the 1200 mg group. Of the patients in the 1200 mg group having plasma levels of greater than 1661 ng/mL, 58% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 39% of patients having plasma levels of less than 1661 ng/mL and 34% of patients receiving the placebo.

## DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

Administration of the same dose of mifepristone can produce widely varying mifepristone blood serum levels in different patients. For the same dose, the blood serum levels can differ by as much as 800% from one patient to another. For those patients with lower blood serum levels, the effectiveness of mifepristone treatment can suffer significantly. The present invention provides a method for optimizing the blood serum levels of mifepristone so that the blood serum levels remain in an efficacious range and the patient receives the necessary treatment.

The method of the present invention optimizes blood serum levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone by first treating the patient with mifepristone. The treatment can be for any appropriate period of time, such as seven or more daily doses over a period of seven or more days. Following

treatment for an appropriate period of time, the serum levels of the patient are tested to determine whether the blood levels of mifepristone are greater than 1300 ng/mL. The daily dose of the patient is then adjusted in order to achieve mifepristone blood levels of greater than 1300 ng/mL.

II. Definitions

The term "amenable to treatment by mifepristone" refers to a condition that is known to be treated by glucocorticoid antagonists such as mifepristone. Conditions such as mental disorders (discussed below) are amenable to treatment by mifepristone.

The term "mental disorder" refers to disorders of the mind that can be treated with a glucocorticoid antagonist such as mifepristone. Mental disorders amenable to treatment by the methods of the present invention include, but are not limited to, a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression.

The term "stress disorder" refers to a psychiatric condition precipitated by exposure to a traumatic or stressful event. Stress disorders include Acute Stress Disorder, Post-Traumatic Stress Disorder, and Brief Psychotic Disorder with Marked Stressor(s).

The term "Acute Stress Disorder" refers to a psychiatric condition in its broadest sense, as defined in American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, D.C., 2000 ("DSM-IV-TR"). The DSM-IV-TR defines "Acute Stress Disorder" as characterized by anxiety, dissociative, and other symptoms occurring within 1 month after exposure to an extreme traumatic stressor. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing Acute Stress Disorder.

The term "Brief Psychotic Disorder with Marked Stressor(s)" refers to a psychiatric condition in its broadest sense, as defined in DSM-IV-TR. The DSM-IV-TR defines "Brief Psychotic Disorder with Marked Stressor(s)" as a sudden but brief onset of psychotic symptoms developing shortly after and apparently in response to one or more stressful events. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing Brief Psychotic Disorder with Marked Stressor(s).

The term "delirium" refers to a psychiatric condition in its broadest sense, as defined in American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, D.C., 2000 ("DSM-IV-TR"). The DSM-IV-TR defines "delirium" as a disturbance of consciousness, developing over a short period of time, accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing delirium.

The term "dementia" refers to a psychiatric condition in its broadest sense, as defined in American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Washington, D.C., 1994 ("DSM-IV"). The DSM-IV defines "dementia" as characterized by multiple cognitive deficits that include impairments in memory and lists various dementias according to presumed etiology. The DSM-IV sets forth a generally accepted standard for such diagnosing, categorizing and treating of dementia and associated psychiatric disorders.

The term "mild cognitive impairment (MCI)" refers to a category of memory and cognitive impairment that is typically characterized by a clinical dementia rating (CDR) of 0.5 (see, e.g., Hughes et al., *Brit. J. Psychiat.* 140:566-572, 1982) and further characterized by memory impairment, but not impaired function in other cognitive domains. Memory impairment is preferably measured using tests such as a "paragraph test". A patient diagnosed with MCI often exhibits impaired delayed recall performance. MCI is typically associated with aging and generally occurs in patients who are 45 years of age or older.

The term "mifepristone" refers to a family of compositions also referred to as RU486, or RU38.486, or 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or 11-beta-(4-dimethylaminophenyl)-17-beta-hydroxy-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or analogs thereof, which bind to the glucocorticoid receptor (GR), typically with high affinity, and inhibit the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to a GR receptor (as discussed within). Salts, hydrates and prodrugs of mifepristone are all within the scope of the present invention.

The term "Post-Traumatic Stress Disorder" refers to a psychiatric condition in its broadest sense, as defined in DSM-IV-TR. The DSM-IV-TR defines "Post-Traumatic Stress Disorder" as characterized by persistent re-experiencing of an extreme traumatic event. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing Post-Traumatic Stress Disorder.

The term "psychotic" as used herein refers to a psychiatric condition in its broadest sense, as defined in the DSM-IV (Kaplan, ed. (1995) supra) and described below. The term "psychotic" has historically received a number of different definitions, ranging from narrow to broadly described. A psychotic condition can include delusions or prominent hallucinations, including prominent hallucinations that the individual realizes are hallucinatory experiences, and those with hallucinations occurring in the absence of insight into their pathological nature. Finally, the term includes a psychotic condition characterized by a loss of ego boundaries or a gross impairment in reality testing. Unlike this definition, which is broad and based primarily on symptoms, characterization of psychosis in earlier classifications (e.g., DSM-II and ICD-9) were more inclusive and focused on the severity of functional impairment (so that a mental disorder was termed "psychotic" if it resulted in "impairment" that grossly interferes with the capacity to meet ordinary demands of life). Different disorders which have a psychotic component comprise different aspects of this definition of "psychotic." For example, in schizophreniform disorder, schizoaffective disorder and brief psychotic disorder, the term "psychotic" refers to delusions, any prominent hallucinations, disorganized speech, or disorganized or catatonic behavior. In psychotic disorder due to a general medical condition and in substance-induced psychotic disorder, "psychotic" refers to delusions or only those hallucinations that are not accompanied by insight. Finally, in delusional disorder and shared psychotic disorder, "psychotic" is equivalent to "delusional" (see DSM-IV, supra, page 273).

Objective tests can be also be used to determine whether an individual is psychotic and to measure and assess the success of a particular treatment schedule or regimen. For example, measuring changes in cognitive ability aids in the diagnosis and treatment assessment of the psychotic patient. Any test known in the art can be used, such as the so-called "Wallach Test," which assesses recognition memory (see below, Wallach (1980) J. Gerontol. 35:371-375). Another example of an objective text which can be used to determine whether an individual is psychotic and to measure efficacy of an antipsychotic treatment is the Stroop Color and Word Test ("Stroop Test") (see Golden, C. J., Cat. No. 30150M, In A Manual for Clinical and Experimental Uses, Stoelting, Wood Dale, Ill.) The Stroop Test is an objective neuropsychiatric

test that can differentiate between individuals with psychosis and those without, and is described in detail below.

The term "psychosis" refers to a psychiatric symptom, condition or syndrome in its broadest sense, as defined in the DSM-IV (Kaplan, ed. (1995) supra), comprising a "psychotic" component, as broadly defined above. The term psychosis can refer to a symptom associated with a general medical condition, a disease state or other condition, such as a side effect of drug abuse (a substance-induced disorder) or as a side effect of a medication. Alternatively, the term psychosis can refer to a condition or syndrome not associated with any disease state, medical condition, drug intake or the like.

Psychosis is typically defined as a mental disorder or condition causing gross distortion or disorganization of a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others to the degree of interfering with his capacity to cope with the ordinary demands of everyday life.

The term "psychotic major depression," also referred to as "psychotic depression" (Schatzberg (1992) Am. J. Psychiatry 149:733-745), "psychotic (delusional) depression" (Ibid.), "delusional depression" (Glassman (1981) supra) and, "major depression with psychotic features" (see the DSM-III-R), refers to a distinct psychiatric disorder which includes both depressive and psychotic features. Individuals manifesting both depression and psychosis, i.e. psychotic depression, are herein referred to as "psychotic depressives." It has been long-recognized in the art as a distinct syndrome, as described, for example, by Schatzberg (1992) supra. Illustrative of this distinctness are studies which have found significant differences between patients with psychotic and nonpsychotic depression in glucocorticoid activity, dopamine-beta-hydroxylase activity, levels of dopamine and serotonin metabolites, sleep measures and ventricle to brain ratios. Psychotic depressives respond very differently to treatment compared to individuals with other forms of depression, such as "non-psychotic major depression." Psychotic depressives have a low placebo response rate and respond poorly to antidepressant therapy alone (without concurrent anti-psychotic treatment). Psychotic depressives are markedly unresponsive to tricyclic (anti-depressive) drug therapy (Glassman, et al. (1975) supra). While psychotic depressives can respond to electroconvulsive therapy (ECT), their response time is relatively slow and the ECT has a high level of related morbidity. Clinical manifestations and diagnostic parameters of "psychotic major depression" is described in detail in the DSM-IV (Kaplan, ed. (1995) supra). Thus, due to its unique pathophysiology, high rate of morbidity and response to treatment, there is great practical need to differentially diagnose and specifically treat psychotic major depression as compared to non-psychotic depression.

The term "optimizing" refers to the process of testing mifepristone blood levels and adjusting the dosage of mifepristone administered to the patient in need in order to achieve mifepristone blood levels above 1300 ng/mL.

The terms "treat", "treating" and "treatment" collectively refer to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being; or, in some situations, preventing the onset of dementia. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation.

The term "testing" refers to determining the mifepristone blood levels in a patient. The testing can be performed by any suitable instrument, such as a plasma sampling collection device capable of detecting mifepristone serum levels.

III. Method for Optimizing Mifepristone Levels

Administration of the same dose of mifepristone to different patients can produce widely varying blood serum levels, varying by up to 800% from one patient to another, resulting in decreased efficacy. The present invention provides a method for optimizing the blood serum levels of mifepristone so that the blood serum levels remain in an efficacious range and the patient receives the necessary treatment.

A. Patients in Need

Patients amenable to treatment with mifepristone according to the method of the present invention suffer from any mental disorder. Exemplary mental disorders include, but are not limited to, a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression.

Stress disorders treatable by the methods of the present invention include, but are not limited to, Acute Stress Disorder (ASD), Post-Traumatic Stress Disorder and Brief Psychotic Disorder with Marked Stressor(s).

Acute Stress Disorder (ASD) is characterized by a constellation of symptoms, lasting at least two days, that appear and resolve within one month of exposure to an extreme traumatic stressor. If symptoms appear or persist beyond one month after exposure to the traumatic stressor, the patient may be considered to suffer from Post-Traumatic Stress Disorder rather than ASD. ASD is a common precursor to Post-Traumatic Stress Disorder, and up to 80% of trauma survivors initially suffering from ASD will meet the diagnostic criteria for Post-Traumatic Stress Disorder six months later (see Brewin et al., Am J Psychiatry 156:360-6, 1999).

Patients develop ASD following exposure to an extreme traumatic stressor (DSM-IV-TR Criterion A). A person must respond to the stressor with intense fear, helplessness, or horror to be diagnosed with ASD. ASD may develop from direct experience of traumatic events, including violent crimes, physical trauma, combat, diagnosis with a life-threatening illness, and natural or manmade disasters. Patients may also develop ASD from witnessing or learning about traumatic events that happen to others, especially family members or close friends. Unexpected exposure to death, dead bodies, or body parts may also induce ASD.

A diagnosis of ASD requires that the person meet several other symptomatic criteria. The person must experience three or more dissociative symptoms in connection with the traumatic stressor (Criterion B). Dissociative symptoms include a subjective sense of numbing or detachment, a reduction in awareness of surroundings, derealization, depersonalization, and dissociative amnesia. Furthermore, ASD requires that the victim persistently re-experience the traumatic event, though recurrent images, thoughts, dreams, illusions, flashbacks, sense of reliving the event, or distress upon exposure to reminders of the event (Criterion C). The person must display marked avoidance of stimuli that arouse recollection of the trauma (Criterion D) and marked symptoms of anxiety or increased arousal (Criterion E). Finally, in addition to the time requirements described above, a diagnosis of ASD requires that the disturbance cause significant distress; or life impairment, and not be due to another psychiatric or physiological condition (Criteria F-H).

Like Acute Stress Disorder, Post-Traumatic Stress Disorder (PTSD) emerges following exposure to an extreme trau-

matic stressor, and is characterized by persistent reexperiencing of the traumatic event, avoidance of stimuli associated with the trauma, and anxiety or increased arousal. The types of traumatic stressors giving rise to PTSD, and the manifestations of PTSD symptoms, are identical to those described above for ASD, but for three differences. First, the dissociative symptoms required for a diagnosis of ASD are not required for a diagnosis of PTSD, although dissociative symptoms may commonly be seen in PTSD patients. Secondly, PTSD need not arise within one month of exposure to the traumatic stressor, and may emerge months or years after the traumatic event. Thirdly, in contrast to the one month maximum duration of symptoms required for a diagnosis of ASD, symptoms must persist for at least one month in order for a diagnosis of PTSD to be made.

A Brief Psychotic Disorder is a short-term (between one day and one month) disturbance involving the sudden onset of at least one psychotic symptom, such as delusions, hallucinations, disorganized speech, or grossly disorganized or catatonic behavior. Brief Psychotic Disorders exclude those induced by a general medical condition. If psychotic symptoms develop shortly after, and apparently in response to, one or more severely stressful events, the disturbance is diagnosed as Brief Psychotic Disorder with Marked Stressor(s) (formerly labeled "brief reactive psychosis" in DSM-III-R). Brief Psychotic Disorder with Marked Stressor(s) is treatable by the glucocorticoid receptor antagonists of the present invention.

Delirium is characterized by disturbances of consciousness and changes in cognition that develop over a relatively short period of time. The disturbance in consciousness is often manifested by a reduced clarity of awareness of the environment. The patient displays reduced ability to focus, sustain or shift attention (DSM-IV-TR diagnostic Criterion A). Accompanying the disturbance in consciousness, delirium patients display a disturbance in cognition (e.g., memory impairment, disorientation, language difficulties) or perceptual disturbances (e.g., misinterpretations, illusions, or hallucinations) (Criterion B). To be considered delirium, these disturbances in consciousness, cognition, or perception should develop over a short period of time and tend to fluctuate during the course of the day (Criterion C).

Delirium may arise from a number of general medical conditions, including central nervous system disorders (e.g., trauma, stroke, encephalopathies), metabolic disorders (e.g., renal or hepatic insufficiency, fluid or electrolyte imbalances), cardiopulmonary disorders (e.g., congestive heart failure, myocardial infarction, shock), and systemic illnesses or effects (e.g., infections, sensory deprivation, and postoperative states). Glucocorticoid receptor antagonists are also effective to treat Substance-Induced Delirium (e.g., delirium induced by substance intoxication or withdrawal, medication side effects, and toxin exposure). Delirium may arise from multiple simultaneous etiologies (e.g., a combination of a general medical condition and substance intoxication) and such delirium, as well as delirium of unknown or unclassified origin, may be treated with the glucocorticoid receptor antagonists of the present invention.

Mild cognitive impairment (MCI) is characterized as a mild impairment of cognition categorized as a CDR of 0.5 that is associated with deficits in a memory task test, such as a paragraph test. An MCI patient is fully oriented, but demonstrates mild consistent forgetfulness. Impairment in cognitive domains other than memory, such as problem solving and judgment is doubtful, if present at all, and, further, the MCI patient does not demonstrate impairment in functioning in the community or at home. A patient with MCI scores normally on standard tests of dementia.

There are various means to diagnose the onset of MCI and to assess the efficacy of treatment using the methods of the invention. These include the administration of psychiatric tests to determine the CDR, the administration of memory tests, and the administration of psychiatric tests for dementia, which are used to exclude a diagnosis of dementia. The results of these test may be considered in conjunction with other objective physical tests as described below. These means are also useful for assessing the efficacy of the methods of the invention in improving memory or decreasing or diminishing further impairment in memory or cognitive decline in a patient with MCI. Subjective and objective criteria can be used to measure and assess the success of a particular GR antagonist, pharmaceutical formulation, dosage, treatment schedule or regimen. The features (symptoms) of and criteria for diagnosing MCI are described, e.g., in Petersen et al., Arch. Neurol. 56:303-308, 1999.

The dementia treated in the methods of the invention encompasses a broad range of mental conditions and symptoms, as broadly described in the DSM-IV. While the practitioner can use any set of prescribed or empirical criteria to diagnose the presence of dementia as an indication to practice the methods of the invention, some illustrative diagnostic guidelines and examples of relevant symptoms and conditions are described below.

The DSM-IV states that dementias typically associated with Alzheimer's disease (dementia of the Alzheimer's type), "vascular dementia" (also known as multi-infarct dementia), or "dementia due to general medical conditions," e.g., human immunodeficiency virus (HIV-1) disease, head trauma, Parkinson's disease, or Huntington's disease (further discussed, below). Dementias can also be "substance-induced persisting dementia," i.e., due to a drug of abuse, a medication, or toxin exposure, "dementia due to multiple etiologies," or a "dementia not otherwise specified" if the etiology is indeterminate.

Psychosis can be manifested as a mental illness in the form of a syndrome or as an element of a variety of disease processes. There are various means to diagnose these various forms of psychosis and assess the success of treatment. These means include classical psychological evaluations in addition to the various laboratory procedures described above. Such means are well-described in the scientific and patent literature, and some illustrative examples are provided below.

The psychosis ameliorated in the methods of the invention encompasses a broad range of mental conditions and symptoms, as broadly described in the DSM-IV (Kaplan, ed. (1995) supra). Psychosis can refer to a symptom associated with a general medical condition, a disease state or other condition, such as a side effect of drug abuse (a substance-induced disorder) or as a side effect of a medication. While the practitioner can use any set of proscribed or empirical criteria to diagnose the presence of a psychosis as an indication to practice the methods of the invention, some illustrative diagnostic guidelines and examples of relevant symptoms and conditions are described below.

Psychiatric conditions, such as psychosis, can be further diagnosed and evaluated using any of the many tests or criteria well-known and accepted in the fields of psychology or psychiatry.

The features (symptoms) of and criteria for diagnosing psychotic disorders, such as psychotic major depression, are further described DSM-IV, supra. While the practitioner can use any criteria or means to evaluate whether an individual is psychotic to practice the methods of the invention, the DSM-

IV sets forth a generally accepted standard for such diagnosing, categorizing and treating of psychiatric disorders, including psychosis. Several illustrative examples of such criteria utilized in the methods of the invention are set forth below.

Psychosis is typically characterized as a mental disorder or condition causing gross distortion or disorganization of a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others to the degree of interfering with his capacity to cope with the ordinary demands of everyday life. In a condition or illness involving psychosis, delusions or hallucinations can be present. The content of the delusions or hallucinations have many depressive themes. In psychotic major depression there can be "mood-congruent" psychotic features, including, for example, delusions of guilt, delusions one deserves punishment (e.g. because of a personal inadequacy or moral transgression), nihilistic delusions (e.g. of world or personal destruction), somatic delusions (e.g. having cancer), or delusions of poverty. Hallucinations, when present in psychotic major depression are usually transient and not elaborate and may involve voices that berate the patient for shortcomings or sins. More rarely, the content of the delusions or hallucinations has no apparent relationship to depressive themes. In this situation these "mood-incongruent" psychotic features include, for example, grandiose delusions.

Psychosis can also include bipolar I disorder with psychotic features, brief psychotic disorder, delusional disorder, shared psychotic disorder, substance induced psychotic disorder and psychotic disorder not otherwise specified.

B. Formulations of Mifepristone

Formulations of the present invention include mifepristone in combination with pharmaceutical excipients. Mifepristone is commercially available from a variety of sources such as Eurolabs Ltd. (London, England). Mifepristone can also be synthesized by one of skill in the art using known synthetic procedures.

The term "mifepristone" refers to a family of compositions also referred to as RU486, or RU38.486, or 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or 11-beta-(4-dimethylaminophenyl)-17-beta-hydroxy-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or analogs thereof, which bind to the GR, typically with high affinity, and inhibit the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to a GR receptor. Chemical names for RU-486 vary; for example, RU486 has also been termed: 11B-[p-(Dimethylamino)phenyl]-17B-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one; 11B-(4-dimethyl-aminophenyl)-17B-hydroxy-17A-(prop -1-ynyl)-estra-4,9-dien-3-one; 17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A -(propynyl-1)-estra-4,9-diene-3-one; 17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A -(propynyl-1)-E; (11B,17B)-11-[4-dimethylamino)-phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one; and 11B-[4-(N,N-dimethylamino) phenyl]-17A-(prop-1-ynyl)-D-4,9-estradiene-17B-ol-3-one. Salts, hydrates and prodrug forms of mifepristone are also useful in the formulations of the present invention.

Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of mifepristone suspended in diluents, such as water, saline or PEG 400; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, microcrystalline cellulose, gelatin, colloidal silicon dioxide, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, e.g., sucrose, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like containing, in addition to the active ingredient, carriers known in the art.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The composition can, if desired, also contain other compatible therapeutic agents. Preferred pharmaceutical preparations can deliver the compounds of the invention in a sustained release formulation.

C. Administration of Mifepristone

The formulations of the present invention provide serum levels of mifepristone of at least 1300 ng/mL. The mifepristone utilized in the pharmaceutical method of the invention is administered at the initial dosage of about 0.001 mg/kg to about 1000 mg/kg daily. A daily dose range of about 0.01 mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 200 mg/kg, or about 1 mg/kg to about 100 mg/kg, or about 10 mg/kg to about 50 mg/kg, can be used. The dosages, however, may be varied depending upon the requirements of the patient and the condition being treated. The dose administered to a patient, in the context of the present invention, should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the practitioner.

Generally, treatment is initiated with six daily doses, with the blood levels tested on the day of the seventh daily dose in order to determine whether the dose used is providing a mifepristone blood level of at least 1300 ng/mL. The testing is also performed to ensure the blood levels are below those afforded by an LD50 dose of about 1000 mg/kg. If the mifepristone blood level is lower than 1300 ng/mL. Additional testing of mifepristone blood levels can be necessary in order to confirm a mifepristone blood level of at least 1300 ng/mL or to adjust the mifepristone daily dose higher. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired. In addition, the interval from initiation of treatment and testing for mifepristone blood levels can be as short as 1 daily dose, or up to 28 daily doses and longer.

Mifepristone can be administered for any period of time, such as 7 daily doses over a period of seven days. Mifepristone can also be administered using more daily doses over a longer period of time, such as via 28 daily doses over a period of 28 days. Longer times for administration of mifepristone are also within the scope of the present invention.

D. Assay for Testing Mifepristone Levels

Mifepristone levels can be determined by any method known in the art. Methods for detecting mifepristone levels include, but are not limited to, radio-immuno assay and mass spectrometry (MALDI, SELDI, LS/MS, LS/MS/MS, among others). Liquid chromatography mass spectrometry (LC/MS

or LC-MS) separates compounds chromatographically before they are introduced to the ion source and mass spectrometer. It differs from GC/MS in that the mobile phase is liquid, usually a combination of water and organic solvents, instead of gas. Most commonly, an electrospray ionization source is used in LC/MS.

Tandem mass spectrometry (MS/MS) involves multiple steps of mass selection or analysis, usually separated by some form of fragmentation. A tandem mass spectrometer is one capable of multiple rounds of mass spectrometry. For example, one mass analyzer can isolate one peptide from many entering a mass spectrometer. A second mass analyzer then stabilizes the peptide ions while they collide with a gas, causing them to fragment by collision-induced dissociation (CID). A third mass analyzer then catalogs the fragments produced from the peptides. Tandem MS can also be done in a single mass analyzer over time as in a quadrupole ion trap. There are various methods for fragmenting molecules for tandem MS, including collision-induced dissociation (CID), electron capture dissociation (ECD), electron transfer dissociation (ETD), infrared multiphoton dissociation (IRMPD) and blackbody infrared radiative dissociation (BIRD). One of skill in the art will appreciate that other assays for testing mifepristone levels are known to one of skill in the art.

In some embodiments, the assay can be performed as follows. Blood is collected from a patient in a vacutainer containing sodium heparin. The blood is centrifuged and the resulting plasma frozen at an appropriate temperature until assay. In some embodiments, the temperature is about −70° C. In other embodiments, other blood components can be collected and stored. Prior to analysis, the plasma is thawed and a fraction of the plasma is mixed with an internal standard in a solvent such as acetonitrile, to obtain a fixed concentration of the standard. In some embodiments, the internal standard can be mifepristone-$d_4$. The concentration of the internal standard is selected in order to be greater than the expected concentration of mifepristone in the plasma. For example, the internal standard can have a concentration of 2000 ng/mL. One of skill in the art will appreciate that other internal standards, and other concentrations, are useful in the present invention.

Base is then added to the sample solution. The base can be any amine or ammonium base, such as ammonium hydroxide. One of skill in the art will appreciate that other bases are useful in the present invention.

Solvent is then added to the solution and the mifepristone (along with the internal standard) are extracted from the plasma. Solvents useful for the extraction of mifepristone include, but are not limited to, hexanes, pentanes, ethers (such as diethylether, tetrahydrofuran and methyl-t-butyl ether (MTBE)), ethyl acetate, chloroform and methylene chloride. One of skill in the art will appreciate that other solvents are useful in the present invention.

Following separation and concentration of the organic layer, the sample is reconstituted in a solvent mixture comprising water, acetonitrile and formic acid. The ratio of the solvent components can vary. In some embodiments, the solvent mixture is water:acetonitrile:formic acid (75:25:0.1, v/v/v). One of skill in the art will appreciate that other solvent mixtures are useful in the present invention.

The sample can then be analyzed by reverse-phase high pressure liquid chromatography (HPLC). In some embodiments, the reverse-phase HPLC is performed using a water:acetonitrile:formic acid (60:40:0.1) mobile phase (isocratic) at a flow rate of 0.3 mL/min. One of skill in the art will appreciate that other mobile phases and flow rates are useful in the present invention.

The reverse-phase HPLC column can be a phenyl column maintained at 50° C. Mifepristone elutes at 4.2 minutes. Following elution, the mobile phase can be nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds detected using a tandem quadrupole mass spectrometer. Mifepristone (molecular weight of 430 g/mol) can be detected at m/z 372.30. The internal standard mifepristone-$d_4$ can be detected at m/z 376.30. The ratio of the mifepristone peak height to the peak height for the internal standard can then be calculated.

The plasma concentration of mifepristone is then calculated by comparing the experimental ratio to a standard curve of mifepristone:mifepristone-$d_4$ peak height ratio v. mifepristone concentration. The standard curve is generated by first measuring the mifepristone:mifepristone-$d_4$ peak height ratios for mifepristone samples at 10, 20, 50, 100, 200, 500, 1000 and 2000 ng/mL where the mifepristone-$d_4$ internal standard has a concentration of 2000 ng/mL. The mifepristone:mifepristone-$d_4$ peak height ratios of these known solutions are then fit to a power equation (Mass Lynx by Micromass, Beverly, Mass.), against which future samples with unknown concentrations of mifepristone are compared.

The plasma levels of mifepristone derivatives such as RU42633, RU42698 and RU42848, among others, can also be determined using the assay described above.

E. Kits for Treating Mental Disorders with Mifepristone

The present invention provides kits. The kits of the present invention comprise seven daily doses and a plasma sampling collection device. The kits of the present invention can also comprise any other component necessary for a kit, such as a container.

Patient plasma can be collected by any known plasma collection device. Some plasma collection devices useful in the present invention include, but are not limited to, vacutainers. The plasma collection devices of the present invention can optionally comprise additives in the device, such as anticoagulants (EDTA, sodium citrate, heparin, oxalate), a gel with intermediate density between blood cells and blood plasma, particles causing the blood to clot, a gel to separate blood cells from serum, thrombin and fluoride, among others.

The kits can also contain additional vessels used for further analysis of the plasma. For example, when the plasma is centrifuged, the centrifuged plasma can be transferred to a vessel, such as a cryostat tube. One of skill in the art will appreciate that other vessels and containers are useful in the present invention.

## IV. EXAMPLES

### Example 1

### Determination of Mifepristone Plasma Level

This example provides a procedure for determining the plasma level of mifepristone in a patient.

Three (3) mL of blood was collected from a patient in a vacutainer containing sodium heparin. The blood was centrifuged and the resulting plasma frozen at −70 to −80° C. until assay. For analysis, the plasma samples were warmed and prepared as follows:

1. Using a pipette, 50.0 μL of the sample was aliquoted into a 16×100-mm glass test tube. When a partial volume aliquot was needed, the aliquot was added to the tube and diluted to full volume with blank human plasma.
2. 20.0 μL of the internal standard, mifepristone-$d_4$ (5.00 μg/mL in acetonitrile), was added to the tube, resulting in 2000.0 ng/mL mifepristone-$d_4$ in plasma.

3. The tube was vortexed for approximately 1 minute.
4. 50.0 μL of 6% ammonium hydroxide was added to the tube.
5. The tube was vortexed for approximately 1 minute.
6. 2.00 mL of MTBE was added to the tube.
7. 2.00 mL of hexane was added to the tube.
8. The tube was vortexed for at least 15 minutes.
9. The tube was centrifuged for at least 10 minutes at 2500 RPM (575×g).
10. The aqueous layer was frozen in a freezer set to maintain −70° C.
11. The upper organic layer was poured into a 13×100-mm polypropylene tube.
12. The organic layer was evaporated in a Turbovap set to 40° C.
13. 200.0 μL of a solution of water:acetonitrile:formic acid (75:25:0.1, v/v/v) was added to the tube.
14. The tube was vortexed for approximately 1 minute.
15. The tube was sonicated for approximately 1 minute.
16. The tube was vortexed for approximately 1 minute.
17. The sample was transferred to a labeled injection vial or well plate.
18. The vial or plate was capped and checked for air bubbles.

The sample was then analyzed by reverse-phase high pressure liquid chromatography using a water:acetonitrile:formic acid (60:40:0.1) mobile phase (isocratic) at a flow rate of 0.3 mL/min. The column was a phenyl column maintained at 50° C. Mifepristone elutes at 4.2 minutes. Following elution, the mobile phase was nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds detected using a tandem quadrupole mass spectrometer. Mifepristone (molecular weight of 430 g/mol) was detected at m/z 372.30. The internal standard mifepristone-$d_4$ was detected at m/z 376.30. The ratio of the mifepristone peak height to the mifepristone-$d_4$ peak height was calculated.

The plasma concentration of mifepristone was then calculated by comparing the experimental ratio to a standard curve of mifepristone:mifepristone-$d_4$ peak height ratio v. mifepristone concentration. The standard curve was generated by first measuring the mifepristone:mifepristone-$d_4$ peak height ratios for mifepristone samples at 10, 20, 50, 100, 200, 500, 1000 and 2000 ng/mL where the mifepristone-$d_4$ internal standard has a concentration of 2000 ng/mL. The mifepristone:mifepristone-$d_4$ peak height ratios of these known solutions were then fit to a power equation (Mass Lynx by Micromass, Beverly, Mass.), and the sample with unknown concentrations of mifepristone was compared.

## Example 2

### Phase III Trial with Three Dose Levels of CORLUX™

This example provides a randomized, double-blind, placebo-controlled, parallel group study of the safety and efficacy of three dose levels of CORLUX™ (Mifepristone) plus an antidepressant vs. placebo plus an antidepressant in the treatment of psychotic symptoms in patients with major depressive disorder with psychotic features (PMD).

The study was a Phase III trial performed using several investigators at several different sites. The objectives were to demonstrate the efficacy and safety of three dose levels of CORLUX (mifepristone) combined with an antidepressant compared to placebo combined with an antidepressant in the treatment of psychotic symptoms in patients with Major Depressive Disorder with Psychotic Features (PMD).

The number of patients was less than 440. Patients eligible for randomization were male or nonpregnant female outpatients, and inpatients, if clinically required, with a diagnosis of Major Depressive Disorder with Psychotic Features (DSM-IV 296.24 or 296.34), and a BPRS Positive Symptom subscale score of at least 12, a BPRS total score of at least 38, and a HAMD-24 score of at least 20.

CORLUX was used as the test drug at 300 (1×300 mg tablet), 600 (2×300 mg tablet), and 1200 mg (4×300 mg tablet) once a day by mouth for the initial 7 days. Appropriate numbers of active and placebo tablets will be given to all dose groups so that each patient takes a total of 4 tablets at each daily dose. The reference drug was a placebo (1, 2, or 4 tablets matching CORLUX 300 mg tablets) once a day by mouth for the initial 7 days.

Up to 440 patients were randomly assigned to receive CORLUX 300, 600, or 1200 mg/day or placebo (in a 1:1:1:1 ratio) each day for 7 days. An antidepressant selected from a prescribed list was started simultaneously with the study drug, and continued to the end of the trial. BPRS and HAM-D assessments were performed at Screen and on Days 0, 7, 14, 28, 42, and 56, and at early termination when it occurred. Safety visits occurred at Days 21 and 35. The patients who are seen as outpatients made daily visits to the clinic setting to receive study medications for the first 7 days. If clinically necessary, a patient was treated as an inpatient.

In addition to the selected antidepressant, continuing benzodiazepines was allowed up to specified dose levels, but antipsychotics, mood stabilizers and additional antidepressants were not allowed during the entire study. If the patient was at imminent risk to him/herself and/or others and therefore could not be adequately treated within the study (e.g., required ECT, new or re-hospitalization for PMD, antipsychotics or mood stabilizers, or a second antidepressant), the patient underwent an early termination visit on the day that rescue therapy was started and completed final efficacy evaluations. If early termination occurred prior to day 35, the patient returned for a safety follow up visit at day 35.

The primary efficacy endpoint was the proportion of patients with at least a 50% reduction from baseline of the BPRS Positive Symptom Subscale (PSS) scores at Days 7 and 56. The secondary endpoints were: (1) the proportion of responders at days 7 and 28; and (2) the mean change from baseline to day 56 in the HAM-D-24 total score.

Adverse events, laboratory assessments including electrocardiograms, and physical examination were used to assess safety.

The criteria for assessing study efficacy objective was the proportion of patients with a reduction of at least 50% from baseline in BPRS Positive Symptom Subscale scores at Days 7 and 56.

## Example 3

### Phase III Trial for Study of the Efficacy and Safety of CORLUX™

This example provides an international, double-blind, placebo-controlled study of the efficacy and safety of CORLUX™ (Mifepristone) vs. placebo in the treatment of psychotic symptoms in patients with Psychotic Major Depression (PMD).

The study was a Phase III trial performed using several investigators at several different international sites. The objective of the trial was to demonstrate the efficacy and safety of CORLUX (mifepristone) combined with an antidepressant compared to placebo combined with an antidepres-

sant in the treatment of psychotic symptoms in patients with Major Depressive Disorder with Psychotic Features (PMD).

The number of patients was 220 evaluable subjects. Patients eligible for randomization were male or non-pregnant female outpatients, or inpatients, if necessary for patient well-being, with a diagnosis of Major Depressive Disorder with Psychotic Features (ICD-10 F32.3 or F33.3 or DSM-IV 296.24 or 296.34). At the screening and baseline visits, patients demonstrated the following severity of illness: BPRS Positive Symptom Subscale (PSS) score ≥12; BPRS total score ≥38, and HAMD-24 total score ≥20.

CORLUX was administered in a 600 mg dose once a day by mouth for the initial 7 days (administered as two 300 mg tablets). Reference drug, dose, dosage regimen, route of administration: Matching placebo was administered once a day by mouth for the initial 7 days.

Up to 280 patients were randomly assigned (1:1 ratio) to receive either CORLUX 600 mg/day or placebo daily for 7 days. After the 7-day dosing period, patients were evaluated at Days 14, 21, 28, 35, 42 and 56. An antidepressant was administered simultaneously with study drug, and continued to the end of the trial (Day 56). BPRS and HAMD-24 assessments were performed at Screen and on Days 0, 7, 14, 28, 42 and 56, or at early termination. A safety visit occurred on Days 21 and 35, and at study termination on Day 56. Subjects treated on an outpatient basis made daily visits to the clinic to receive study medication for the first 7 days. Subjects were treated on an inpatient basis for as long as deemed clinically necessary by the investigator.

In addition to the selected antidepressant, concomitant benzodiazepine treatment was allowed up to specified dose levels. Antipsychotics, mood stabilizers and a second antidepressant were prohibited during the entire study. If the patient was at imminent risk to him/herself and/or others and therefore could not be adequately treated within the study (i.e., required ECT, new or re-hospitalization for PMD, antipsychotics or mood stabilizers, or a second antidepressant), the patient underwent an early termination visit on the day that rescue therapy was started, and completed procedures listed for the day 56 termination visit, including final efficacy evaluations. If early termination occurred prior to day 35, the patient returned for a safety follow-up visit at regularly scheduled day 35.

The Primary efficacy endpoint was determined by the proportion of patients with ≥50% reduction from baseline on the BPRS-PSS at Days 7 and 28. Key secondary efficacy endpoints include (1) the proportion of patients with ≥50% reduction from baseline on the BPRS-PSS at Days 7 and 56; and (2) change from baseline on the HAMD-24 at Day 56.

Adverse events, laboratory assessments including electrocardiograms, and physical examination were used to assess safety.

Example 4

Treatment of Male Patient with PMD

A 50 year-old male, weighing 175 pounds, presents to physician with psychotic major depression (PMD). The physician prescribes 300 mg of mifepristone for seven daily doses over a period of seven days. One week later on the day of the seventh daily dose, three (3) mL of blood are collected from the patient and analyzed as described above in the specification. The dose of mifepristone is then adjusted, if necessary, to achieve mifepristone blood levels of greater than 1300 ng/mL. The mifepristone dose can be adjusted a single time to achieve mifepristone blood levels of greater than 1300 ng/mL. Alternatively, several adjustments to the mifepristone dose can be necessary to safely achieve mifepristone blood levels of greater than 1300 ng/mL.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference.

What is claimed is:

**1**. A method for optimizing levels of mifepristone in a patient suffering from a disorder amenable to treatment by mifepristone, the method comprising:

treating the patient with seven or more daily doses of mifepristone over a period of seven or more days;

testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and

adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

**2**. The method of claim **1**, wherein the disorder is a member selected from the group consisting of a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression.

**3**. The method of claim **2**, wherein the stress disorder is a member selected from the group consisting of Acute Stress Disorder, Post-Traumatic Stress Disorder and Brief Psychotic Disorder with Marked Stressor(s).

**4**. The method of claim **1**, wherein each of the seven or more daily doses of mifepristone are administered orally.

**5**. The method of claim **1**, wherein the patient is treated with 28 or more daily doses over a period of 28 or more days.

**6**. The method of claim **1**, wherein the testing is performed by a plasma sampling collection device suitable for detecting mifepristone serum levels.

**7**. The method of claim **1**, wherein the adjusting step comprises increasing the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

* * * * *

# EXHIBIT B

US010195214B2

(12) **United States Patent**
**Belanoff**

(10) **Patent No.: US 10,195,214 B2**
(45) **Date of Patent: *Feb. 5, 2019**

(54) **CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS**

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See application file for complete search history.

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(Continued)

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(57) **ABSTRACT**

Applicant provides methods of treating diseases including Cushing's syndrome and hormone-sensitive cancers by concomitant administration of a glucocorticoid receptor antagonist (GRA) and steroidogenesis inhibitors, and by concomitant administration of a GRA and CYP3A inhibitors. Applicant provides methods of treating diseases including Cushing's syndrome and hormone-sensitive cancers by concomitant administration of mifepristone and ketoconazole. Subjects treated with CYP3A inhibitors or steroidogenesis inhibitors may suffer from toxicity or other serious adverse reactions; concomitant administration of other drugs would be expected to increase the risk of such toxicity and adverse reactions. Applicant has surprisingly found that GRAs may be administered to subjects receiving CYP3A inhibitors or steroidogenesis inhibitors such as ketoconazole without increasing risk adverse reactions; for example, Applicant has found that mifepristone may be concomitantly administered with ketoconazole (a CYP3A inhibitor and a steroidogenesis inhibitor), providing safe concomitant administration of the GRA and ketoconazole. In embodiments, the GRA dose may be reduced.

**13 Claims, 1 Drawing Sheet**

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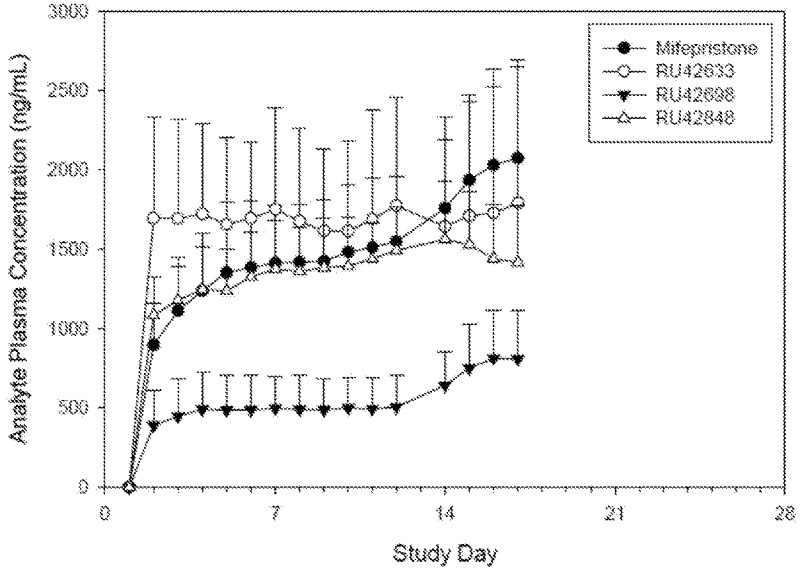

Analyte Plasma Concentration (ng/mL)
Study Day
Mifepristone
RU42633
RU42698
RU42848
0
500
1000
1500
2000
2500
3000
0
7
14
21
28

FIG. 1

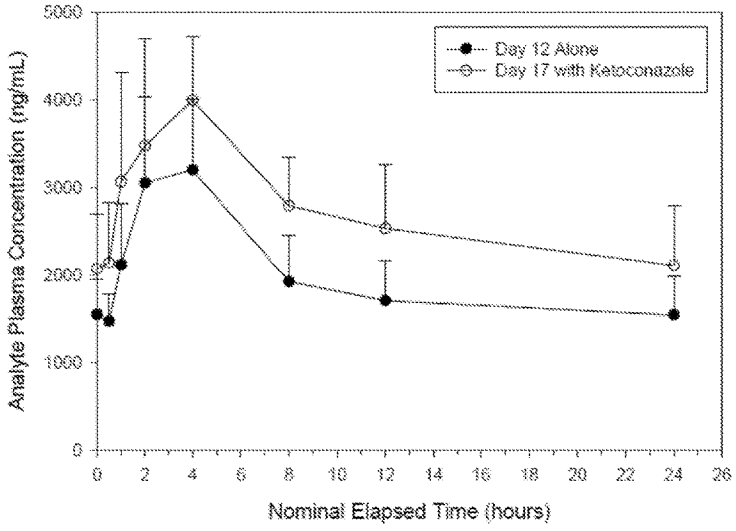

Analyte Plasma Concentration (ng/mL)
Nominal Elapsed Time (hours)
Day 12 Alone
Day 17 with Ketoconazole
0
1000
2000
3000
4000
5000
0
2
4
6
8
10
12
14
16
18
20
22
24
26

FIG. 2

# CONCOMITANT ADMINISTRATION OF GLUCOCORTICOID RECEPTOR MODULATORS AND CYP3A INHIBITORS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of, and priority to, U.S. Provisional Application Ser. No. 62/465,772, filed Mar. 1, 2017, and U.S. Provisional Application Ser. No. 62/466,867, filed Mar. 3, 2017, the entire contents of both of which applications are hereby incorporated by reference in their entireties.

## BACKGROUND

Steroid molecules, such as steroid hormones, play an important role in bodily functions and in bodily responses to infectious and other diseases, and to the environment. Many steroid molecules are synthesized in the body, or are produced from molecules consumed in the diet. Steroid molecules which act as hormones in the body include estrogen, progesterone, testosterone, and cortisol. Some steroid molecules have medicinal effects. Inhibition of steroid synthesis or metabolism can be useful in the treatment of some disorders.

Cortisol, a steroid molecule, plays an important role in many bodily functions. Cortisol exerts effects by binding to cortisol receptors, which are present in most tissues in the body. However, dysregulation of cortisol may have adverse effects on a subject. For example, Cushing's syndrome, caused by excess levels of cortisol, is characterized by symptoms including elevated blood pressure, elevated blood glucose, increased weight, increased mid-section perimeter, other pre-diabetic symptom, a "moon-face" facial appearance, immune suppression, thin skin, acne, depression, hirsutism, and other symptoms. Clinical manifestations of Cushing's syndrome include abnormalities in glucose control, requirement for anti-diabetic medication, abnormalities in insulin level, abnormal psychiatric symptoms, cushingoid appearance, acne, hirsutism, and increased or excessive body weight, and other symptoms.

One effective treatment of cortisol dysregulation is to block the binding of cortisol to cortisol receptors, or to block the effect of cortisol binding to cortisol receptors. Mifepristone binds to cortisol receptors, and acts to block such binding and to block the effect of cortisol on tissues. Mifepristone is 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)-estra-4,9-dien-3-one).

Another effective treatment of cortisol dysregulation is to reduce the synthesis of cortisol, e.g., by reducing or blocking steroid synthesis. A "steroidogenesis inhibitor" is a compound which reduces or blocks the synthesis of steroid molecules (including, e.g., cortisol) when administered to a subject. Steroidogenesis inhibitors include, for example, ketoconazole, metyrapone, etomidate, and other drugs.

Many enzymes are involved in steroid synthesis and in steroid metabolism, including cytochrome P450 enzymes, encoded by CYP genes. Inhibiting steroid synthesis may lower the levels of steroids, including, e.g., cortisol, in the blood. For example, CYP3A enzymes play important roles in the synthesis of steroid hormones such as cortisol.

However, many drugs inhibit the levels or actions of CYP3A gene products (termed "inhibit CYP3A"). The following drugs inhibit CYP3A: ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole, among many drugs which inhibit CYP3A. For example, the following drugs strongly inhibit CYP3A (i.e., increase AUC (area under the concentration-time curve) by 10-fold or greater of sensitive index substrates), either alone or in combination with other drugs: boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir, ritonavir, itraconazole, ketoconazole, lopinavir, paritaprevir, ombitasvir, dasabuvir, posaconazole, saquinavir, telaprevir, tipranavir, troleandomycin, and voriconazole.

Ketoconazole is an exemplary and an important steroidogenesis inhibitor and is a strong CYP3A inhibitor. Ketoconazole (chemical name: 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl] methoxy]phenyl]piperazine) is administered for the treatment of fungal infections; it also affects steroid metabolism by inhibiting steroidogenesis, and has anti-glucocorticoid and anti-androgen effects due to its interference with enzymatic conversion of cholesterol to hormones such as cortisol and testosterone. Ketoconazole has effects on liver enzymes and the gastrointestinal (GI) tract, among other effects (Fleseriu and Castinetti, *Pituitary* 19:643-653 (2016)).

Ketoconazole inhibits steroid synthesis and is thus useful in the treatment Cushing's syndrome; in the treatment of prostate cancer and other androgen-sensitive cancers; to reduce estrogen or progesterone production (e.g., in patients with hormone-sensitive cancers such as breast cancer and ovarian cancer); and in other treatments.

A drug such as ketoconazole is typically metabolized and excreted by a subject over time following administration. An effective dose is determined based on the expected amounts of metabolism and excretion of the drug. Changes in the amounts or rates of metabolism and/or excretion of a drug will affect the dose required, and may make an otherwise safe dose, if metabolism or excretion changes, into either a less, or ineffective dose, or a more effective or even toxic dose.

However, although sometimes clinically useful, ketoconazole may have adverse, including seriously toxic, effects (Fleseriu and Castinetti, *Pituitary* 19:643-653 (2016)). The U.S. Food and Drug Administration issued a Drug Safety Communication (Jul. 26, 2013 Safety Announcement regarding Nizoral® (ketoconazole)) warning of potentially fatal liver damage associated with oral ketoconazole treatment and warning of the risk of adrenal insufficiency, also a potentially fatal disorder. The Safety Announcement warned: "Nizoral tablets can cause liver injury, which may potentially result in liver transplantation or death." The Safety Announcement further stated: "Nizoral tablets may interact with other drugs a patient is taking and can result in serious and potentially life-threatening outcomes, such as heart rhythm problems." Thus, ketoconazole can be quite toxic if administered in excessive amounts, or if it is administered to sensitive individuals, particularly when administered systemically (as opposed, e.g., to topically). This toxicity can lead to liver damage (sometimes requiring liver transplantation). Other CYP3A inhibitors, including, e.g., itraconazole, ritonavir, and other CYP3A inhibitors as discussed herein, may have similar effects and may require similar warnings.

The simultaneous, or nearly simultaneous (e.g., concomitant) presence of two drugs in a subject may alter the effects of one or the other, or both, drugs. Such alterations are termed drug-drug interactions. For example, the required

dose of a drug is often strongly affected by taking the amount and rate of its degradation in, and elimination from, the body (e.g., by liver or kidney action). However, the presence of a second drug in the body, which is also being acted upon by the liver and kidney, can have significant effects on the amount and rate of degradation of the first drug, and can increase the amount of the first drug that remains in the body at a given time beyond the amount that would have been present at that time in the absence of the second drug. Thus, the presence of a second drug can often increase the effective dose of the first drug. Where the first drug has toxic side effects, such an increase in effective dose of the first drug may lead to dangerous toxicity that would not have been expected were the second drug not present.

Concomitant administration of different drugs often leads to adverse effects since the metabolism and/or excretion of each drug may reduce or interfere with the metabolism and/or excretion of the other drug(s), thus increasing the effective concentrations of those drugs as compared to the effective concentrations of those drugs when administered alone. Thus, concomitant administration of drugs is often expected to increase the risk of toxic effects of one or both of the co-administered drugs. Some drugs, such as ketoconazole, present risk of liver damage (including severe cases including liver failure and even requiring liver transplants) and other toxic effects when administered alone; the risk of such toxic effects is believed to be increased when other drugs are concomitantly administered. Where a drug, such as ketoconazole, is known to present a high risk of toxic effects, clinicians will typically avoid its concomitant administration with other drugs.

However, patients often require treatment with multiple drugs, so that the potential toxicity of drugs such as ketoconazole present disadvantages that can have deleterious consequences for the patient who requires ketoconazole treatment, or may require foregoing the use of ketoconazole or of some other drug which may have otherwise been required for successful treatment.

Accordingly, improved methods of treatment allowing the administration of other drugs along with CYP3A inhibitors (such as, e.g., ketoconazole) and along with steroidogenesis inhibitors (such as, e.g., ketoconazole) are desired.

## SUMMARY

Applicant discloses herein that CYP3A inhibitors such as, e.g., ketoconazole, may be concomitantly administered with glucocorticoid receptor modulators (GRMs) such as the GR antagonik (GRA) mifepristone. Such concomitant administration of a CYP3A inhibitor such as ketoconazole and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, and may allow the reduction in the amount of a GRM, or of a CYP3A inhibitor, administered to the subject; such reduction may reduce the risk of toxic effects of the CYP3A inhibitor concomitantly administered with the GRM. In embodiments, the CYP3A inhibitor is a strong CYP3A inhibitor. Such concomitant administration of a CYP3A inhibitor such as ketoconazole and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, may allow the reduction in the amount of GRM administered to the subject, and may allow the reduction in the amount of a CYP3A inhibitor administered to the subject; such reductions may improve treatment of the patient and may reduce the risk of toxic effects of the CYP3A inhibitor.

Applicant discloses herein that steroidogenesis inhibitors may be concomitantly administered with glucocorticoid receptor modulators (GRMs) such as the GR antagonist (GRA) mifepristone. Such concomitant administration of a steroidogenesis inhibitor and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, and may allow concomitant administration of a GRA and a steroidogenesis inhibitor, may allow the reduction of the amount of GRM administered to the subject, or may allow the reduction in the amount of a steroidogenesis inhibitor administered to the subject; such reductions may reduce the risk of toxic effects of the steroidogenesis inhibitor. Such concomitant administration of a steroidogenesis inhibitor and a GRM such as mifepristone is believed to be safe for the subject, and to provide the therapeutic benefits of both drugs to the subject, and may allow the reduction in the amount of GRM or of a steroidogenesis inhibitor administered to the subject; such reduction may improve treatment of the subject and may reduce the risk of toxic effects of the steroidogenesis inhibitor.

For example, Applicant has surprisingly discovered that mifepristone may be administered to patients concomitantly receiving ketoconazole. For example ketoconazole may be administered to patients previously, or concomitantly, also receiving mifepristone so that the patient concomitantly receives ketoconazole and mifepristone. Such concomitant administration of ketoconazole and mifepristone is typically safe for the patient, provides the therapeutic benefits of both drugs to the patient, and may allow the reduction in the amount of mifepristone administered to the subject; such reduction may provide an effective dose of mifepristone that is a lower dose, yet still provides similar plasma mifepristone levels as, and may be as effective as, the dose of mifepristone administered in the absence of ketoconazole. Such concomitant administration of ketoconazole and mifepristone provides the therapeutic benefits of both drugs to the patient, may allow a reduction in the amount of mifepristone administered to the patient, and may allow the reduction in the amount of ketoconazole administered to the patient; such reduction may reduce the risk of toxic effects of ketoconazole, and may improve the treatment of the patient.

Applicant's surprising discovery is believed to apply to patients suffering from a disease or disorder and receiving a CYP3A inhibitor, including a strong CYP3A inhibitor such as ketoconazole; such patients suffering from a disease or disorder may be safely administered a GRM, such as mifepristone, concomitantly with the administration of a CYP3A inhibitor such as ketoconazole. Such concomitant administration is believed to be safe for the patient. For example, concomitant administration of ketoconazole and mifepristone surprisingly does not increase the risk of ketoconazole toxicity in the patient, and is believed to be safe for the patient. In particular, Applicant discloses herein that Cushing's syndrome patients receiving ketoconazole may be safely administered mifepristone concomitantly with the administration of ketoconazole. Such concomitant administration of ketoconazole and mifepristone to a patient suffering from Cushing's syndrome is believed to be safe for the patient suffering from Cushing's syndrome, which is characterized by hypercortisolism. Patients suffering from Cushing's syndrome, such as those suffering from endogenous Cushing's syndrome, may suffer hyperglycemia secondary to hypercortisolism. Concomitant administration of a GRA (such as, e.g., mifepristone) and a CYP3A inhibitor (such as, e.g., ketoconazole) as disclosed herein is believed to be safe,

and to be suitable for controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome.

In embodiments, a method of treating a patient with Cushing's syndrome, the patient currently taking a GRA at an original dosage, comprises reducing the amount of GRA from said original dosage to an adjusted dosage that is less than the original dosage when the patient is receiving concomitant administration of a CYP3A inhibitor. In embodiments, a method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome, the patient currently taking a GRA at an original dosage, comprises reducing the amount of GRA from said original dosage to an adjusted dosage that is less than the original dosage when the patient is receiving concomitant administration of a CYP3A inhibitor. In embodiments of such methods, the adjusted dosage is less than the original dosage by at least an amount selected from about 5%, 10%, 15%, 20%, 25%, 30%, $33^{1/3}$%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, $66^{2/3}$%, 70%, 75%, 80%, 85%, and 90% of the original dosage. In embodiments, the adjusted dosage is less than the original dosage by at least 10% of the original dosage. In embodiments, the adjusted dosage is less than the original dosage by at least 25% of the original dosage. In embodiments, the adjusted dosage is less than the original dosage by at least $33^{1/3}$% of the original dosage. In embodiments, the adjusted dosage is less than the original dosage by at least 50% of the original dosage.

In embodiments, where a GRM such as mifepristone would be prescribed at a first GRM dose, the amount of the GRM (such as mifepristone) administered, when co-administered with a steroidogenesis inhibitor or CYP3A inhibitor such as ketoconazole, may be reduced to a reduced GRM dose that has a smaller amount of GRM as compared to the first GRM dose yet provide effective treatment at the reduced GRM dose co-administered with a steroidogenesis inhibitor such as ketoconazole. In embodiments, the clinical status of a subject receiving a reduced GRM dose concomitantly with a steroidogenesis inhibitor may be monitored for clinical response, e.g., for clinical response to the GRM (such as mifepristone). Monitoring for clinical response may include monitoring for clinical effect of the GRM, including clinical efficacy of the GRM; for clinical effect of a steroidogenesis inhibitor of CYP3A inhibitor; for possible adverse reaction to a steroidogenesis inhibitor or CYP3A inhibitor, or the use of a steroidogenesis inhibitor or CYP3A inhibitor in combination with the GRM; for possible side-effects of a steroidogenesis inhibitor or CYP3A inhibitor; for possible side-effects of the use of a steroidogenesis inhibitor or CYP3A inhibitor in combination with the GRM; or combinations thereof.

In embodiments, the reduced GRM dose may be increased as necessary and as safe for the patient according to such monitoring of the patient. In embodiments, the reduced GRM dose may be titrated upwards as necessary and as safe for the subject according to such monitoring of the patient in order to achieve effective treatment of Cushing's syndrome while remaining safe for the patient with regard to possible adverse effects of the concomitant administration of the GRM and the CYP3A inhibitor, or of the concomitant administration of the GRM and the steroidogenesis inhibitor.

In embodiments, where a GRM such as mifepristone would be prescribed at a first GRM dose, the amount of the GRM (such as mifepristone) administered, when co-administered with a CYP3A inhibitor, including a strong CYP3A inhibitor such as ketoconazole, may be reduced to a reduced GRM dose that has a smaller amount of GRM as compared to the first GRM dose yet provide effective treatment at the reduced GRM dose co-administered with a CYP3A inhibitor such as ketoconazole. In embodiments, the clinical status of a patient receiving a reduced GRM dose concomitantly with a CYP3A inhibitor may be monitored, e.g., for clinical effect of the GRM, for clinical effect of the CYP3A inhibitor, for possible adverse reaction to the CYP3A inhibitor or its use in combination with the GRM, for possible side-effects of the CYP3A inhibitor or its use in combination with the GRM, or combinations thereof. In embodiments, the reduced GRM dose may be increased as necessary and as safe for the patient according to such monitoring of the patient. In embodiments, the reduced GRM dose may be titrated upwards as necessary and as safe for the patient according to such monitoring of the patient in order to achieve effective treatment of Cushing's syndrome while remaining safe for the patient with regard to possible adverse effects of the concomitant administration of the GRM and the CYP3A inhibitor.

Accordingly, Applicant discloses herein that a steroidogenesis inhibitor may be administered to patients concomitantly receiving administration of a GRM. Accordingly, Applicant discloses herein that a CYP3A inhibitor may be administered to patients concomitantly receiving administration of a GRM. For example, Applicant discloses herein that ketoconazole, a steroidogenesis inhibitor and a CYP3A inhibitor, may be administered to patients suffering from a disease or disorder, such as, e.g., Cushing's syndrome, who are concomitantly receiving administration of a GRM such as mifepristone. Such concomitant administration of both a GRA (such as mifepristone) and a CYP3A inhibitor (such as ketoconazole) may be administered to a patient suffering from endogenous Cushing's syndrome to control hyperglycemia secondary to hypercortisolism in the patient.

Accordingly, Applicant discloses herein that GRMs may be administered to subjects previously, or concomitantly, also receiving administration of a steroidogenesis inhibitor or a CYP3A inhibitor. For example, Applicant discloses herein that GRMs may be administered to subjects suffering from a disease or disorder, such as, e.g., Cushing's syndrome, who previously, or are concomitantly, also receiving administration of a steroidogenesis inhibitor or a CYP3A inhibitor such as ketoconazole. Applicant discloses methods for concomitant administration of a GRM and a steroidogenesis or CYP3A inhibitor such as ketoconazole useful for treating a subject in need of such administration. Subjects in need of such administration include subjects suffering from a disease or disorder, and include subjects suffering from Cushing's syndrome. Applicant further discloses that such administration of a GRM and a steroidogenesis or a CYP3A inhibitor such as ketoconazole is typically safe for the subject, and provides the therapeutic benefits of both drugs to the subject. In embodiments, such concomitant administration of a steroidogenesis or a CYP3A inhibitor such as ketoconazole and a GRM may allow the reduction in the amount of GRM, or of a steroidogenesis or a CYP3A inhibitor such as ketoconazole, that is administered to the subject; such reductions may reduce the risk of toxic effects of a steroidogenesis or a CYP3A inhibitor such as ketoconazole, such as, e.g., reduce the risk of liver damage to the subject. The GRM may be, e.g., mifepristone.

Applicant has surprisingly discovered that a steroidogenesis or a CYP3A inhibitor such as ketoconazole may be concomitantly administered with GRMs, such as GRAs, so that concomitant administration of a steroidogenesis or a CYP3A inhibitor such as ketoconazole and a GRA for

example may provide safe and effective treatment of a patient in need of treatment. A patient receiving concomitant administration of a steroidogenesis or a CYP3A inhibitor such as ketoconazole and a GRA may be, for example, a patient in need of treatment for Cushing's syndrome (including Cushing's Disease), breast cancer, prostate cancer, ovarian cancer, or other hormone-sensitive cancer. In embodiments, such a patient in need of treatment may receive concomitant administration of a steroidogenesis or a CYP3A inhibitor such as ketoconazole and a GRA, such as mifepristone. In embodiments, such a patient in need of treatment may receive concomitant administration of ketoconazole and mifepristone.

The methods, compositions, and kits disclosed herein are suitable for use in treating patients suffering from Cushing's syndrome (including Cushing's Disease); or from prostate cancer and other androgen-sensitive cancers; or from breast cancer, ovarian cancer, or other hormone-sensitive cancer (e.g., cancer sensitive to estrogen or progesterone); and are suitable for use in treating subjects suffering from other diseases, disorders, or syndromes.

In embodiments of the methods disclosed herein, a patient currently receiving a GRM, such as mifepristone, is also concomitantly administered a steroidogenesis or a CYP3A inhibitor such as ketoconazole. In embodiments of the methods disclosed herein, a patient currently receiving a GRM, such as mifepristone, as treatment for a condition characterized by excess steroid levels, or as treatment of a condition that is treated by reducing steroid levels or by reducing steroid effects, is also concomitantly administered a steroidogenesis or a CYP3A inhibitor such as ketoconazole, whereby the patient is treated for that condition. In embodiments, the condition is characterized by excessive cortisol levels. In embodiments, the condition is hyperglycemia secondary to hypercortisolism, e.g., in a patient suffering from endogenous Cushing's syndrome. In embodiments, the condition is cancer, and may be a hormone-sensitive cancer. In embodiments, the hormone sensitive cancer is prostate cancer, breast cancer, or ovarian cancer.

In embodiments of the methods disclosed herein, a patient currently receiving a steroidogenesis or a CYP3A inhibitor such as ketoconazole is also concomitantly administered a GRM. In embodiments of the methods disclosed herein, a patient currently receiving a steroidogenesis or a CYP3A inhibitor such as ketoconazole as treatment for a condition characterized by excess steroid levels, or as treatment of a condition that is treated by reducing steroid levels or by reducing steroid effects, is also concomitantly administered a GRM, whereby the patient is treated for that condition. In embodiments, the condition is characterized by excessive cortisol levels. In embodiments, the condition is hyperglycemia secondary to hypercortisolism, e.g., in a patient suffering from endogenous Cushing's syndrome. In embodiments, the condition is hyperglycemia secondary to hypercortisolism, e.g., in a patient suffering from endogenous Cushing's syndrome. In embodiments, the condition is cancer, and may be a hormone-sensitive cancer. In embodiments, the hormone sensitive cancer is prostate cancer, breast cancer, or ovarian cancer.

Thus, in embodiments of the methods disclosed herein, a patient in need of treatment for a condition is concomitantly administered both a GRM (such as mifepristone) and a steroidogenesis or a CYP3A inhibitor (such as ketoconazole), whereby the patient is treated for that condition. In embodiments, the condition is characterized by excessive cortisol levels. In embodiments, the condition is hyperglycemia secondary to hypercortisolism, e.g., in a patient suffering from endogenous Cushing's syndrome. In embodiments, the condition is cancer, and may be a hormone-sensitive cancer. In embodiments, the hormone sensitive cancer is prostate cancer, breast cancer, or ovarian cancer.

In embodiments, the amount of GRM administered concomitantly with a steroidogenesis or a CYP3A inhibitor is the same amount, or substantially the same amount, of GRM previously administered to the patient prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, the amount of GRM administered concomitantly with a steroidogenesis or a CYP3A inhibitor is less than the amount of GRM previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, administration of a reduced amount of GRM administered concomitantly with a steroidogenesis or a CYP3A inhibitor is an effective amount of GRM; in embodiments, the reduced amount of GRM administered concomitantly with a steroidogenesis or a CYP3A inhibitor is as effective as the amount of GRM previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. The GRM may be mifepristone. The steroidogenesis or a CYP3A inhibitor may be ketoconazole.

In embodiments, the amount of steroidogenesis or a CYP3A inhibitor administered concomitantly with the GRM is the same amount, or substantially the same amount, of steroidogenesis or CYP3A inhibitor previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, the amount of steroidogenesis or CYP3A inhibitor administered concomitantly with the GRM is less than the amount of steroidogenesis or CYP3A inhibitor previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, administration of a reduced amount, of steroidogenesis or CYP3A inhibitor administered concomitantly with a GRM is an effective amount of steroidogenesis or CYP3A inhibitor; in embodiments, the reduced amount of steroidogenesis or CYP3A inhibitor administered concomitantly with a GRM is as effective as the amount of steroidogenesis or CYP3A inhibitor previously administered to the subject prior to concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor. The GRM may be mifepristone. The steroidogenesis or CYP3A inhibitor may be ketoconazole.

Concomitant administration of a GRM and steroidogenesis or a CYP3A inhibitor may be administration of a GRM followed within a short time by administration of a steroidogenesis or a CYP3A inhibitor. In embodiments, concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be administration of mifepristone followed within a short time by administration of ketoconazole. Concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be administration of a steroidogenesis or a CYP3A inhibitor followed within a short time by administration of a GRM. In embodiments, concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be administration of ketoconazole followed within a short time by administration of mifepristone. Concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be simultaneous administration of a GRM and a steroidogenesis or a CYP3A inhibitor. In embodiments, concomitant administration of a GRM and a steroidogenesis or a CYP3A inhibitor may be simultaneous administration of mifepristone and ketoconazole.

In embodiments, the GRM is a steroidal GRM, such as, e.g., mifepristone. In embodiments, the GRM is a non-steroidal GRM. In embodiments, the GRM is a glucocorticoid receptor antagonist (GRA). In embodiments, the GRA is a steroidal GRA. In embodiments, the GRA is mifepristone. In embodiments, the GRA is a non-steroidal GRA. In embodiments, the GRA is a non-steroidal GRA selected from a GRA having a cyclohexyl-pyrimidine backbone, GRA having a fused azadecalin backbone, a GRA having a heteroaryl ketone fused azadecalin backbone, and a GRA having an octahydro fused azadecalin backbone.

In embodiments, a patient is concomitantly administered a GRM and ketoconazole; in embodiments, the GRM is mifepristone. In embodiments, concomitant administration comprises simultaneous administration of a GRM and ketoconazole to a patient, where the GRM is mifepristone. In embodiments, the amount of ketoconazole administered concomitantly with the mifepristone is the same amount, or substantially the same amount, of ketoconazole previously administered to the subject prior to concomitant administration of mifepristone and ketoconazole. In embodiments, the amount of ketoconazole administered concomitantly with the mifepristone is less than the amount of ketoconazole previously administered to the subject prior to concomitant administration of mifepristone and ketoconazole.

Accordingly, in embodiments, Applicant discloses herein a method for treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome, said patient receiving a first dose of a glucocorticoid receptor antagonist (GRA), said method comprising: concomitantly administering to the patient a dose of a CYP3A inhibitor and a reduced dose of said GRA, wherein said reduced GRA dose consists of a GRA dose that is less than the first GRA dose, whereby the patient is treated for Cushing's syndrome or a condition associated with Cushing's syndrome by concomitant administration of said CYP3A inhibitor and a reduced dose said GRA. Conditions associated with Cushing's syndrome include, without limitation, hyperglycemia secondary to hypercortisolism, e.g., hyperglycemia secondary to hypercortisolism in a patient suffering from endogenous Cushing' syndrome. Conditions associated with Cushing's syndrome also include, without limitation, hyperglycemia secondary to hypercortisolism in an adult Cushing's syndrome patient who has type 2 diabetes mellitus or glucose intolerance. Conditions associated with Cushing's syndrome further include, without limitation, hyperglycemia secondary to hypercortisolism in an adult Cushing's syndrome patient who has a) type 2 diabetes mellitus or glucose intolerance, and b) has failed surgery or is not a candidate for surgery.

In embodiments, the dosage of said reduced GRA dose is less than the dosage of said first GRA dose by at least an amount selected from about 5%, 10%, 15%, 20%, 25%, 30%, $33^{1/3}$%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, $66^{2/3}$%, 70%, 75%, 80%, 85%, and 90% of the first GRA dose. In embodiments, the dosage of said reduced GRA dose is less than the dosage of said first GRA dose by about 300 milligrams (mg) of said GRA. In embodiments, the dosage amount of said first GRA dose is 600 mg or higher of said GRA. In embodiments, said reduced GRA dose is a GRA dose selected from the group of GRA doses consisting of about 1500 milligrams (mg) GRA, about 1200 mg GRA, about 900 mg GRA, and about 600 mg GRA. In embodiments, said reduced GRA dose is 900 mg of the GRA. In embodiments, said reduced GRA dose is 600 mg of the GRA. In embodiments, the reduced GRA dose is a daily GRA dose. In embodiments, the methods further comprise titrating upwards the dosage of the reduced GRA dose. In embodiments, such titrating upwards comprises increasing the dosage of the reduced GRA dose in increments of 300 milligrams (mg) of GRA. In embodiments, the interval of time between upward titration of a reduced dose, or of an upwardly titrated reduced dose, and a subsequent upward titration of a dosage of the reduced dose of mifepristone is selected from one week, two weeks, three weeks, and four weeks. In embodiments, the methods include monitoring the patient for clinical response to the GRA. In embodiments, such titrating upwards follows a determination that said reduced GRA dose is associated with a decrease in clinical response to the GRA. In embodiments, monitoring the patient for clinical response to the GRA comprises monitoring the patient for glucose control, anti-diabetic medication requirement, insulin level, psychiatric symptoms, cushingoid appearance, acne, hirsutism, body weight, or combinations thereof. In embodiments, such titrating upwards is capped at a dosage level of 900 milligrams per day. In embodiments, such titrating upwards is capped at a dosage level of 600 milligrams per day. In embodiments of the methods disclosed herein, the reduced GRA dose is a daily dose of 900 mg mifepristone. In embodiments of the methods disclosed herein, the reduced GRA dose is a daily dose of 600 mg mifepristone.

Embodiments of the methods disclosed herein are directed to treating a patient suffering from Cushing's syndrome or a condition associated with Cushing's syndrome. In embodiments, the patient suffering from Cushing's syndrome or a condition associated with Cushing's syndrome is a patient suffering from a condition associated with endogenous Cushing's syndrome. In embodiments, treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome comprises treating a patient who is suffering from hyperglycemia secondary to hypercortisolism. In embodiments, treating patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome comprises treating hyperglycemia secondary to hypercortisolism in a Cushing's syndrome patient having type 2 diabetes mellitus or glucose intolerance. In embodiments, treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome comprises treating hyperglycemia secondary to hypercortisolism in a Cushing's syndrome patient, said patient a) having type 2 diabetes mellitus or glucose intolerance, and b) having failed surgery or is not a candidate for surgery. In embodiments, treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome comprises administering mifepristone to control hyperglycemia secondary to hypercortisolism in an adult Cushing's syndrome patient who has a) type 2 diabetes mellitus or glucose intolerance, and b) has failed surgery or is not a candidate for surgery.

In embodiments, Applicant discloses herein a method for treating a patient who is suffering from Cushing's syndrome or a condition associated with Cushing's syndrome, said patient receiving a first dose of a glucocorticoid receptor antagonist (GRA), said method comprising: concomitantly administering to the patient a dose of said CYP3A inhibitor and a first dose of a glucocorticoid receptor antagonist (GRA), whereby the patient is treated for Cushing's syndrome or a condition associated with Cushing's syndrome by concomitant administration of said CYP3A inhibitor and said GRA. In embodiments, the first GRA dose is selected from a GRA dose no greater than 900 milligrams (mg) per day of the GRA, and no greater than 600 mg per day of the

GRA. In embodiments, the patient had been administered a dose of the CYP3A inhibitor prior to said administering of said first GRA dose. In embodiments, said concomitant administration of the CYP3A inhibitor and said GRA comprises administration of said first GRA dose to a patient having detectable levels of said CYP3A inhibitor, wherein said patient had been administered a dose of the CYP3A inhibitor prior to said administration of said first GRA dose. In embodiments, methods further comprise titrating upwards the dosage of a subsequent GRA dose, wherein the dosage of said subsequent GRA dose is a greater amount of GRA than the amount of GRA of the first GRA dose. In embodiments, such titrating upwards comprises increasing the dosage of the subsequent GRA dose in increments of 300 milligrams (mg) of GRA. In embodiments, the interval of time between upward titration of a subsequent GRA dose, or of an upwardly titrated subsequent GRA dose, and a subsequent upward titration of the dosage of the subsequent GRA dose is selected from one week, two weeks, three weeks, and four weeks.

In embodiments of the methods disclosed herein, the CYP3A inhibitor is a strong CYP3A inhibitor selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, and voriconazole. In embodiments, the CYP3A inhibitor is ketoconazole.

In embodiments of the methods disclosed herein, the GRA is mifepristone.

The methods disclosed herein provide advantages including expanded treatment options for patients suffering from conditions including Cushing's syndrome, Cushing's Disease, prostate cancer, breast cancer, ovarian cancer, and other conditions.

The methods disclosed herein provide advantages including improved treatments for patients suffering from conditions including Cushing's syndrome, Cushing's Disease, prostate cancer, breast cancer, ovarian cancer, and other conditions, where such improved treatments may include the ability to alter the amount of a GRM, such mifepristone, administered to the patient by administering a GRM such as mifepristone concomitantly with ketoconazole. In embodiments, such improved treatments include the ability to reduce the amount of a GRM, such as mifepristone, administered to a subject.

The methods disclosed herein provide advantages including improved treatments for patients suffering from conditions including Cushing's syndrome, Cushing's Disease, prostate cancer, breast cancer, ovarian cancer, and other conditions, where such improved treatments may include the ability to alter the amount of ketoconazole administered to the patient by administering a GRM such as mifepristone concomitantly with ketoconazole. In embodiments, such improved treatments include the ability to reduce the amount of ketoconazole administered to a subject and thus to reduce risk of toxic effects of the ketoconazole.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the mean and standard deviation of mifepristone and its metabolites RU42633, RU42698, and RU42848 measured in healthy male volunteers prior to administration of mifepristone on days one through seventeen. Ketoconazole was also administered on days thirteen-seventeen.

FIG. **2** shows the plasma concentration profile of mifepristone measured in healthy male volunteers on day twelve (before administration of ketoconazole) and on day seventeen (the fifth day of ketoconazole administration).

## DETAILED DESCRIPTION

Ketoconazole strongly inhibits corticosteroid synthesis; thus, ketoconazole strongly reduces cortisol levels in subjects administered ketoconazole. However, there is concern over its use, for example, due to potential hepatoxicity (see, e.g., Castinetti et al., J Clin Endocrinol Metab 99(5):1623-1630 (2014)).

According to the U.S. Food and Drug Administration (FDA) definition strong CYP3A inhibitors are expected to increase the AUC of other drugs by greater than five-fold. Ketoconazole is identified by the FDA as a strong CYP3A inhibitor (See FDA web posting: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers).

Surprisingly, as disclosed herein, concomitant administration of mifepristone and ketoconazole causes only a small increase in the plasma levels of mifepristone, and does not cause the large increases that would have been expected for such concomitant administration.

Applicant has surprisingly found that concomitant administration of mifepristone and ketoconazole causes only a small increase in the AUC and in the Cmax of mifepristone in subjects receiving mifepristone alone for twelve days, and then administered both mifepristone and ketoconazole concomitantly. The Cmax of mifepristone administered concomitantly with ketoconazole is increased by less than two-fold (a mere 28% increase in mifepristone Cmax) and the AUC of mifepristone administered concomitantly with ketoconazole is increased by less than two-fold (a mere 38% increase in mifepristone AUC) in subjects receiving 600 mg mifepristone per day who then are given 400 mg ketoconazole (200 mg twice per day)).

Also surprisingly, as disclosed herein, concomitant administration of ketoconazole and mifepristone also caused smaller increases in ketoconazole levels than would be expected. The Cmax of ketoconazole administered concomitantly with mifepristone is increased by less than four-fold (365% increase in ketoconazole Cmax) and the AUC of ketoconazole administered concomitantly with mifepristone is increased by less than three-fold (253% increase in ketoconazole AUC) when comparing ketoconazole levels on the first day of concomitant administration of both drugs as compared to the ketoconazole levels in subjects on the fifth day of receiving 400 mg ketoconazole (200 mg twice per day) concomitantly with 600 mg mifepristone per day.

Ketoconazole is a strong inhibitor of steroidogenesis; thus it is believed that ketoconazole may serve as an examplar for other strong inhibitors of steroidogenesis and that these results indicate that mifepristone, and other glucocorticoid receptor modulators, including other glucocorticoid receptor antagonists, may be safely administered concomitantly with steroidogenesis inhibitors according to the methods disclosed herein.

Ketoconazole is a strong inhibitor of CYP3A enzymes; thus it is believed that ketoconazole may serve as an examplar for other strong inhibitors of CYP3A enzymes and that these results indicate that mifepristone, and other glucocorticoid receptor modulators, including other glucocorticoid receptor antagonists, may be safely administered concomitantly with CYP3A enzyme inhibitors according to the methods disclosed herein.

Applicant discloses herein methods for the safe concomitant administration of both a glucocorticoid receptor modulator (GRM) and steroidogenesis inhibitor to a subject. Applicant discloses herein the surmising finding that both a GRM such as mifepristone and a steroidogenesis inhibitor such as ketoconazole may be safely administered to a subject at the same, or nearly the same, time (i.e., the GRM and the steroidogenesis inhibitor may be concomitantly administered).

Applicant discloses herein methods for the safe concomitant administration of both a glucocorticoid receptor modulator (GRM) and CYP3A inhibitor to a subject. Applicant discloses herein the surprising finding that both a GRM such as mifepristone and a CYP3A inhibitor such as ketoconazole may be safely administered to a subject at the same, or nearly the same, time (i.e., the GRM and the CYP3A may be concomitantly administered).

Applicant discloses herein the surprising finding that a subject receiving ketoconazole, which is a steroidogenesis inhibitor and is a CYP3A inhibitor, may also be safely administered an effective dose of mifepristone, which is a glucocorticoid receptor modulator (GRM), e.g., a glucocorticoid receptor antagonist (GRA). Applicant also discloses herein the surprising finding that a subject receiving mifepristone, which is a glucocorticoid receptor modulator (GRM), e.g., a glucocorticoid receptor antagonist (GRA), may also be safely administered ketoconazole, which is a steroidogenesis inhibitor and is a CYP3A inhibitor.

In embodiments of the methods disclosed herein, a subject receiving a GRM (such as, e.g., a glucocorticoid receptor antagonist (GRA) such as mifepristone) may be safely administered an effective dose of a steroidogenesis inhibitor such as ketoconazole. In embodiments of the methods disclosed herein, a subject may be safely administered ketoconazole and a reduced dose of a GRM, where the reduced dose of a GRM is an effective dose of GRM that is a smaller GRM dose than the GRM dose administered in the absence of a steroidogenesis inhibitor such as ketoconazole. In embodiments of the methods disclosed herein, a subject may be safely administered a GRM and a reduced dose of a steroidogenesis inhibitor such as ketoconazole, where the reduced dose of the steroidogenesis inhibitor is an effective dose of the steroidogenesis inhibitor that is a smaller dose than the a steroidogenesis inhibitor dose administered in the absence of the GRM. In embodiments of the methods disclosed herein, a subject receiving a steroidogenesis inhibitor such as, e.g., ketoconazole, may be safely administered an effective dose of a GRM, such as, e.g., mifepristone. In embodiments of the methods disclosed herein, a subject receiving a GRM, such as, e.g., mifepristone, may be safely administered an effective dose of a steroidogenesis inhibitor such as, e.g., ketoconazole.

These methods may be applied to subjects suffering from diseases or disorders as well as other subjects, including subjects suffering from Cushing's syndrome. Such concomitant administration of a steroidogenesis inhibitor such as ketoconazole with a GRM would have been expected to produce toxic side effects due to, e.g., an adverse effect on steroidogenesis inhibitor metabolism due to the added GRM (e.g., where the steroidogenesis inhibitor is ketoconazole, a previously safe ketoconazole dose would have been expected to be a toxic dose in the presence of added GRM (e.g., mifepristone)).

In particular, Applicant discloses herein that patients suffering from a disease or disorder and receiving ketoconazole may be safely administered mifepristone concomitantly with the administration of ketoconazole. Such concomitant administration of ketoconazole and mifepristone surprisingly does not increase the risk of toxicity in the patient, and is believed to be safe for the patient. In particular, Applicant discloses herein that Cushing's syndrome patients receiving ketoconazole may be safely administered mifepristone concomitantly with the administration of ketoconazole. Such concomitant administration of ketoconazole and mifepristone surprisingly does not increase the risk of toxicity in humans, and is believed to be safe for a patient suffering from Cushing's syndrome.

Thus, Applicant discloses herein surprising and useful methods for concomitant administration of a steroidogenesis inhibitor such as, e.g., ketoconazole, and a GRM such as, e.g., mifepristone, which provide the benefits of improved treatment without substantially increased risk of adverse treatment side-effects. For example, Applicant provides herein surprising and useful methods for concomitant administration of ketoconazole and mifepristone, which provide the benefits of both drugs without substantially increased risk of ketoconazole toxicity, which can have serious adverse effects on the liver.

Thus, contrary to the expectation that the presence of a GRM such as mifepristone along with a steroidogenesis inhibitor (e.g., ketoconazole) in a patient would increase the toxicity of the steroidogenesis inhibitor beyond that expected for such a dose of steroidogenesis inhibitor alone, Applicant has discovered that administering a) both a GRM (e.g., mifepristone) and a steroidogenesis inhibitor (e.g., ketoconazole) to a subject, or b) administering a GRM (e.g., mifepristone) to a subject who has recently been given a steroidogenesis inhibitor (e.g., ketoconazole), or c) administering a steroidogenesis inhibitor (e.g., ketoconazole) soon after GRM (e.g., mifepristone) administration to a subject, concomitant administration of a GRM and a steroidogenesis inhibitor does not increase the expected toxicity of the steroidogenesis inhibitor. In embodiments, concomitant administration of a steroidogenesis inhibitor and a GRM allows for administration of an effective dose of GRM that is a reduced GRM dose as compared to the GRM dose administered in the absence of the steroidogenesis inhibitor.

In embodiments, concomitant administration of ketoconazole and mifepristone allows for administration of an effective dose of mifepristone that is a reduced dose of mifepristone as compared to the mifepristone dose administered in the absence of ketoconazole. For example, Applicant has discovered that concomitant administration of mifepristone and ketoconazole makes it possible to reduce the dose of mifepristone while maintaining sufficient mifepristone levels for effective therapy for the patient. Such a reduction in mifepristone dose provides the benefit of reducing the amount of mifepristone administered to the subject. Embodiments in which a subject is concomitantly administered ketoconazole and mifepristone allow for mifepristone dose reduction (as compared to the mifepristone dose in the absence of ketoconazole) include, e.g., Cushing's syndrome and hormone-sensitive cancers such as breast, ovarian, and prostate cancer, and other disorders susceptible of treatment by mifepristone.

In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is at least about 5% less than the original dose of mifepristone, where the original dose of mifepristone is the dose the subject had been, or would have been, administered in the absence of ketoconazole co-administration. In embodiments, the reduced dose of mifepristone is a dose of mifepristone that is at least about 10% less than the original dose of mifepristone; and may be

a dose of mifepristone that is at least about 15%, or about 20%, or about 22%, or about 23%, or about 25%, or about 28%, or about 29%, or about 33%, or about 38%, or about 40%, or about 50%, or about 66%, or about 75% less than the original dose of mifepristone.

In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is 300 mg less mifepristone than the amount of the original dose of mifepristone. In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is an amount of mifepristone that is an integer multiple of 300 mg mifepristone less than the amount of the original dose of mifepristone. In embodiments, the integer of the integer multiple is selected from the integers 1, 2, 3, 4, and 5.

In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is about 900 mg mifepristone; or is about 600 mg mifepristone; or is about 300 mg mifepristone. In embodiments, the reduced dose of mifepristone administered to a subject also concomitantly receiving ketoconazole is a dose of mifepristone that is about 300 mg mifepristone administered only every other day; or is about 300 mg mifepristone administered every third day; or is about 300 mg mifepristone administered every fourth day. For example, where the original dose of mifepristone is about 1500 mg per day, the reduced dose of mifepristone may be about 1200 mg of mifepristone administered every day; or may be about 900 mg of mifepristone administered every day; or may be about 600 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every day. For example, where the original dose of mifepristone is about 1200 mg per day, the reduced dose of mifepristone may be about 900 mg of mifepristone administered every day; or may be about 600 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every day. For example, where the original dose of mifepristone is about 900 mg per day, the reduced dose of mifepristone may be about 600 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every other day. For example, where the original dose of mifepristone is about 600 mg per day, the reduced dose of mifepristone may be about 300 mg of mifepristone administered every day; or may be about 300 mg of mifepristone administered every other day; or may be about 300 mg of mifepristone administered every third day. For example, where the original dose of mifepristone is about 300 mg per day, the reduced dose of mifepristone may be about 300 mg of mifepristone administered every other day; or may be about 300 mg of mifepristone administered every third day; or may be about 300 mg of mifepristone administered every fourth day.

In embodiments in which a subject has been receiving about 1800 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 1500 mg mifepristone per day; may be about 1200 mg mifepristone per day; may be about 900 mg mifepristone per day; may be about 600 mg mifepristone per day; may be about 300 mg mifepristone per day; may be about 300 mg mifepristone every other day; or may be about 300 mg mifepristone every third day. In embodiments in which a subject has been receiving about 1500 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 1200 mg mifepristone per day; may be about 900 mg mifepristone per day; may be about 600 mg mifepristone per day; may be about 300 mg mifepristone every other day; or may be about 300 mg mifepristone every third day. In embodiments in which a subject has been receiving about 1200 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 900 mg mifepristone per day; may be about 600 mg mifepristone per day; may be about 300 mg mifepristone per day; may be about 300 mg mifepristone every other day; or may be about 300 mg mifepristone every third day. In embodiments in which a subject has been receiving about 900 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 600 mg mifepristone per day; may be about 300 mg mifepristone per day; may be about 300 mg mifepristone every other day; or may be about 300 mg mifepristone every third day. In embodiments in which a subject has been receiving about 600 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 300 mg mifepristone per day; may be about 300 mg mifepristone every other day; may be about 300 mg every third day; or may be about 300 mg mifepristone every fourth day. In embodiments in which a subject has been receiving about 300 mg mifepristone per day, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be about 300 mg mifepristone every other day; may be about 309 mg every third day; or may be about 300 mg mifepristone every fourth day.

In embodiments in which a subject has been receiving a first dose of mifepristone (e.g. a daily dose of mifepristone of about 1800 mg/day, or about 1500 mg/day, or about 1200 mg/day, or about 900 mg/day, or about 600 mg/day, or about 300 mg/day), and concomitant administration of mifepristone and ketoconazole is indicated, the subject may be administered a reduced dose of mifepristone, where the amount of the reduced dose is less than the original mifepristone dose by about 300 mg mifepristone per day, and the subject may be monitored for clinical effects of the drugs, including monitoring for clinical response to mifepristone. In embodiments in which a subject has been receiving a first dose of mifepristone (e.g. a daily dose of mifepristone of about 1800 mg/day, or about 1500 mg/day, or about 1200 mg/day, or about 900 mg/day, or about 600 mg/day, or about 300 mg/day), and concomitant administration of mifepristone and ketoconazole is indicated, the subject may be administered a reduced dose of mifepristone, where the amount of the reduced dose is less than the original mifepristone dose by about 300 mg mifepristone per day, and the reduced dose of mifepristone may be subsequently titrated upwards (i.e., increased in subsequent dose administrations) in increments of about 300 mg mifepristone. In embodiments, such upward titration of the reduced dose in increments of 300 mg/day may be subjected to a maximum daily dosage of about 600 mg/day, or of about 900 mg/day, or of about 1200 mg/day, or of about 1500 mg/day. In embodiments, such upward titration of the dosage of the reduced daily dose of mifepristone administered per day is capped at a maximum daily dose, wherein said maximum daily dose is selected from the group consisting of 900 milligrams (mg) mifepristone per day and 600 mg mifepristone per day.

The subject may be monitored for clinical effects of the drugs, e.g., for clinical response to the GRA (e.g., mifepris-

tone), adverse events, side-effects of any drug, at any stage or at all stages, of such incremental upward titration of the mifepristone dosage. The interval of time between administration of a reduced dose, or of an upwardly titrated reduced dose, and an upward titration of a dose of mifepristone may be an interval selected from two days, four days, one week, two weeks, one month, two months, and three months. In embodiments, the interval of time between upward titration of a reduced dose, or of an upwardly titrated reduced dose, and a subsequent upward titration of a dosage of the reduced dose of mifepristone is selected from one week, two weeks, three weeks, and four weeks. Monitoring the patient for clinical response may include monitoring the patient (e.g., to identify or determine if there are changes in) for glucose control, anti-diabetic medication requirement, insulin level, psychiatric symptoms, cushingoid appearance, acne, hirsutism, and monitoring the body weight of the patient (e.g., to identify or determine if there are changes in any one or more of these symptoms and characteristics).

In embodiments in which a subject has been receiving a first dose of mifepristone (e.g. a daily dose of mifepristone of about 1800 mg/day, or about 1500 mg/day, or about 1200 mg/day, or about 900 mg/day, or about 600 mg/day, or about 300 mg/day), and concomitant administration of mifepristone and ketoconazole is indicated, the subject may be administered a reduced dose of mifepristone, where the amount of the reduced dose is less than the original mifepristone dose, and the reduced dose of mifepristone may be about 1500 mg mifepristone per day, or about 1500 mg/day, or about 1200 mg/day, or about 900 mg/day, or about 600 mg/day, or about 300 mg/day; and the subject may be monitored for clinical response to the GRA, or for other clinical effects of the drugs. In such embodiments, the reduced dose of mifepristone may be subsequently titrated upwards (i.e., increased in subsequent dose administrations) in increments of about 300 mg mifepristone. In embodiments, such upward titration of the reduced dose in increments of 300 mg/day may be subjected to a maximum daily dosage of about 600 mg/day, or of about 900 mg/day, or of about 1200 mg/day, or of about 1500 mg/day. In embodiments, such upward titration of the dosage of the reduced daily dose of mifepristone administered per day is capped at a maximum daily dose, wherein said maximum daily dose is selected from the group consisting of 900 milligrams (mg) mifepristone per day and 600 mg mifepristone per day.

The subject may be monitored for clinical response to the drugs, including e.g., clinical response to the GRA (e.g., mifepristone), for adverse events, side-effects of any of the drugs, at any stage, or at all stages, of such incremental upward titration of the mifepristone dosage. Upward titration of a reduced dose of mifepristone may be performed every two days, or every four days, or every week, or every two weeks, or every month, or every two months. In embodiments, the interval of time between upward titration of a reduced dose, or of an upwardly titrated reduced dose, and a subsequent upward titration of a dosage of the reduced dose of mifepristone is selected from one week, two weeks, three weeks, and four weeks.

Applicant discloses herein that concomitant treatment with both mifepristone and ketoconazole may lead to small increases in plasma levels of mifepristone as measured by Cmax and as measured by AUC. For example, as disclosed in Table 3 below, concomitant administration of mifepristone and ketoconazole led to about 28% (27.59%, or about 30%) increase in mifepristone Cmax and about 38% (38.01%, about 40%) increase in mifepristone AUC. Thus, in embodiments, a mifepristone dose administered to a subject receiving concomitant administration of mifepristone and ketoconazole may be reduced in compensation for such a small increase in mifepristone plasma levels. In embodiments in which a subject has been receiving mifepristone, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be reduced by about 22% of the original dose of mifepristone. In embodiments in which a subject has been receiving mifepristone, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be reduced by about 23% of the original dose of mifepristone. In embodiments in which a subject has been receiving mifepristone, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be reduced by about 28% of the original dose of mifepristone. In embodiments in which a subject has been receiving mifepristone, and concomitant administration of mifepristone and ketoconazole is indicated, the reduced dose of mifepristone may be reduced by about 29% of the original dose of mifepristone. In embodiments, the reduced dose of mifepristone is a dose of mifepristone that is at least about 90% of the original dose of mifepristone; and may be a dose of mifepristone that is at least about 85%, or about 80%, or about 78%, or about 77%, or about 75%, or about 72%, or about 71%, or about 67%, or about 62%, or about 60%, or about 50%, or about 34%, or about 25% of the original dose of mifepristone.

Applicant further discloses herein that, since mifepristone provides added therapeutic benefit synergistic with that of ketoconazole, concomitant administration of mifepristone and ketoconazole makes it possible to reduce the dose of ketoconazole while maintaining mifepristone levels effective for therapy for a patient. Such a reduction in ketoconazole dose provides the benefit of reducing the risk of toxic side-effects associated with all ketoconazole treatments. Thus, concomitant administration of ketoconazole and mifepristone, by allowing reduced ketoconazole dose, provides improved, synergistic therapeutic benefits. In embodiments, such ketoconazole dose reduction may be used to wean the patient off ketoconazole, leading to lower and lower ketoconazole doses, thereby reducing the risk of ketoconazole toxicity. In embodiments, such ketoconazole dose reduction may be used to wean the patient off ketoconazole, leading to lower and lower ketoconazole doses, with concomitant upward adjustment of mifepristone dosage as needed, ultimately leading to treatment with mifepristone alone and cessation of ketoconazole treatment (lessening the risk of liver damage and other toxicities). Embodiments in which concomitant administration of ketoconazole and mifepristone may lead to ketoconazole dose reduction (as compared to the ketoconazole dose in the absence of mifepristone) include, e.g., Cushing's syndrome and hormone-sensitive cancers such as breast, ovarian, and prostate cancer, and other disorders susceptible of treatment by mifepristone.

In embodiments, concomitant administration of ketoconazole and mifepristone allows for administration of an effective dose of ketoconazole that is a reduced dose of ketoconazole as compared to the ketoconazole dose administered in the absence of mifepristone. For example, Applicant discloses herein that concomitant administration of mifepristone and ketoconazole makes it possible to reduce the dose of ketoconazole while maintaining effective therapy for the patient. Such a reduction in ketoconazole dose provides the benefit of reducing the amount of ketoconazole administered to the subject. Embodiments in which a subject is concomitantly administered ketoconazole and mifepristone allow for ketoconazole dose reduction (as compared to

the ketoconazole dose in the absence of mifepristone) include, e.g., Cushing's syndrome and hormone-sensitive cancers such as breast, ovarian, and prostate cancer, and other disorders susceptible of treatment by ketoconazole and other steroidogenesis inhibitors.

In embodiments, the reduced dose of ketoconazole administered to a subject also concomitantly receiving mifepristone is a dose of ketoconazole that is at least about 5% less than the original dose of ketoconazole, where the original dose of ketoconazole is the dose the subject had been, or would have been, administered in the absence of mifepristone co-administration. In embodiments, the reduced dose of ketoconazole is a dose of ketoconazole that is at least about 10% less than the original dose of ketoconazole; and may be a dose of ketoconazole that is at least about 15%, or about 20%, or about 25%, or about 33%, or about 50%, or about 66%, or about 75% less than the original dose of ketoconazole.

Applicant provides definitions of some terms used in the present disclosure.

Definitions

The abbreviations used herein have their conventional meaning within the chemical and biological arts.

"Patient", "patient in need", "subject", "subject in need" and the like refer to a person having, or suspected of having, a disease or condition which may be treated by administration of a therapeutic drug.

As used herein, the term "Cushing's syndrome" refers to an array of symptoms caused by excess cortisol. Cushing's syndrome includes endogenous Cushing's syndrome and ectopic Cushing's syndrome. Such symptoms include, for example, elevated blood pressure, elevated blood glucose, increased weight (typically in the mid-section, and in the face causing a characteristic "moon-face"), immune suppression, thin skin, acne, depression, hirsutism, and other symptoms.

As used herein, "Cushing's Disease" refers to pituitary-dependent Cushing's syndrome, e.g., excess cortisol caused by pituitary abnormality (typically a pituitary tumor). Cushing's Disease is thus a disease that is a particular type of Cushing's syndrome. The term Cushing's syndrome thus includes reference to Cushing's Disease.

As used herein, a "patient suffering from Cushing's syndrome" refers to any patient suffering from Cushing's syndrome, including endogenous Cushing's syndrome; Cushing's Disease; or a condition associated with Cushing's syndrome. A condition associated with Cushing's syndrome may be, without limitation, a condition associated with endogenous Cushing's syndrome; hyperglycemia secondary to hypercortisolism; a condition of hypercortisolism in an endogenous Cushing's syndrome patient, said patient having type 2 diabetes mellitus or glucose intolerance; a condition of hyperglycemia secondary to hypercortisolism in an endogenous Cushing's syndrome patient, said patient having type 2 diabetes mellitus or glucose intolerance and having failed surgery; hyperglycemia secondary to hypercortisolism in an endogenous Cushing's syndrome patient, said patient having type 2 diabetes mellitus or glucose intolerance and having failed surgery or who is not a candidate for surgery; and other conditions associated with Cushing's syndrome.

"Treat", "treating" and "treatment" refer to any indicia of success in the treatment or amelioration of a pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; or improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination; histopathological examination (e.g., analysis of biopsied tissue); laboratory analysis of urine, saliva, tissue samples, serum, plasma, or blood; or imaging.

As used herein, "treating a patient who is suffering from Cushing's syndrome", or treating a subject who is suffering from Cushing's syndrome", or similar phrases refer to, without limitation, treating a patient suffering from Cushing's syndrome, including endogenous Cushing's syndrome; treating a patient suffering from Cushing's Disease; or treating a patient suffering from a condition associated with Cushing's syndrome. A condition associated with Cushing's syndrome is discussed above. For example, treating a patient who is suffering from Cushing's syndrome may include administering mifepristone or other GRA to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.

As used herein, the term "administration" refers to the delivery of a drug or other therapeutic into the body of a patient in need of treatment by the drug or therapeutic, effective to achieve a therapeutic effect. Administration may be by any suitable route of administration, including, for example, oral administration; intravenous administration; subcutaneous administration; parenteral administration; intra-arterial administration; nasal administration; topical administration; and other routes of administration.

As used herein, the terms "percent", "%" and "weight percent" when applied to a dosage administered to a subject, all refer to a percentage taken by comparing the weight of a first dose to that of a second dose, and multiplying the resulting decimal fraction by 100. Thus, for example, where an original mifepristone dose is 1200 milligrams (mg), a dose that is reduced by 50% is a dose of 600 mg mifepristone; and where an original mifepristone dose is 600 milligrams (mg), a dose that is reduced by 50% is a dose of 300 mg mifepristone; and so forth.

As used herein, the phrases "less than x by at least", "less than x by at least about", and the like refer to amounts equal to and less than the x, where x is a number. For example, the phrase "less than the original dosage by at least 25%" refers to dosage amounts that include 25% less than the original dosage as well as other percentages (e.g., 26%, 28%, etc.) less than the original dosage amount.

As used herein, the terms "effective amount," "amounts effective," therapeutic amount", and "therapeutically effective amount" refer to an amount or amounts of one or more pharmacological agents effective to treat, eliminate, or mitigate at least one symptom of the disease being treated. In some cases, "effective amount," "amounts effective," "therapeutic amount", and "therapeutically effective amount" can refer to an amount of a functional agent or of a pharmaceutical composition useful for exhibiting a detectable therapeutic or inhibitory effect.

As used herein, the term "simultaneously or sequentially administering" refers to administration of two compounds, such as a GRA and a CYP3A inhibitor, such that the two compounds are in the body at the same time in therapeutically effective amounts.

As used herein, "concomitant" means at the same, or nearly the same, time, and "concomitantly" refers to actions performed at the same, or nearly the same, time. As used herein, he terms "concurrent" and "concomitant" are equiva-

lent and may be used interchangeably. The adverbs "concurrently" and "concomitantly" are equivalent and may be used interchangeably.

As used herein, the term "concomitant administration" of two or more drugs means administering two or more drugs at the same, or nearly the same, time. Concomitant administration of two or more drugs provides therapeutically effective amounts of the two or more drugs in the system of the subject at the same time. Concomitant administration includes administration of a GRA to a patient who has previously been administered a drug, such as a CYP3A inhibitor or a steroidogenesis inhibitor, and therapeutically effective levels of the CYP3A inhibitor or steroidogenesis inhibitor remain in the patient when the patient is administered the GRA (e.g., when the patient is administered mifepristone), and includes administration of a CYP3A inhibitor or a steroidogenesis inhibitor to a patient who has previously been administered a drug, such as a GRA, and therapeutically effective levels of the GRA remain in the patient when the patient is administered the CYP3A inhibitor or steroidogenesis inhibitor.

As used herein, "concomitantly administering drugs" means that two or more drugs are administered to a subject at the same, or nearly the same, time. Drugs that are concomitantly administered will each be present in therapeutically effective amounts in the system of the subject at the same time. Nearly the same time means that only a short amount of time separates two events, such as administration of a first drug and the administration of a second drug.

Events or actions that are "simultaneous" or that occur or are performed "simultaneously" are events that occur or are performed at the same time.

As used herein, "at the same time" means that two events occur or are performed within about five minutes of each other.

As used herein, "nearly the same time" means that two events occur or are performed within about a short time of each other.

As used herein, a "short time", a "short amount of time", a "short period of time", and the like mean a time that is less than about two hours, or less than about one hour, or less than about 45 minutes, or less than about 30 minutes, or less than about 20 minutes, or less than about 10 minutes, or less than about 7 minutes.

As used herein, the term "clinical effect" means changes in symptoms or signs characteristic of, or indicative of, a clinical condition or disorder. For example, where a subject is treated for Cushing's syndrome, including Cushing's Disease, a clinical effect may be a change in any one or more of blood pressure, blood glucose, other pre-diabetic symptom, weight, mid-section perimeter, facial characteristics (e.g., change in "moon-face" appearance), immune function, skin thickness, acne, depression or other mood symptom, hirsutism, and other symptoms.

As used herein, "monitoring for clinical response", e.g., monitoring a patient for clinical response to a GRA such as mifepristone, may include monitoring the patient (e.g., to identify or determine if there are changes in) for glucose control, anti-diabetic medication requirement, insulin level, psychiatric symptoms, cushingoid appearance, acne, hirsutism, and monitoring the body weight of the patient (e.g., to identify or determine if there are changes in any one or more of these symptoms and characteristics). Monitoring for clinical response may also include monitoring a patient for adverse events, for side-effects of any drug (including a GRA, a CYP3A inhibitor, a steroidogenesis inhibitor, and combinations of these). Thus, monitoring for clinical response may include monitoring for clinical effect of a drug such as a GRM, including clinical efficacy of the GRM; for clinical effect of a steroidogenesis inhibitor or CYP3A inhibitor; for possible adverse reaction to a steroidogenesis inhibitor or CYP3A inhibitor; for possible adverse reaction to the use of a steroidogenesis inhibitor or CYP3A inhibitor in combination with the GRM; for possible side-effects of a steroidogenesis inhibitor or CYP3A inhibitor, or their use in combination with the GRM; or combinations thereof.

As used herein, the term "AUC" means the area under the plasma concentration-time curve, and serves as a measure of the plasma levels of a drug in a subject to whom the drug has been administered.

As used herein, the term "$C_{max}$" means the maximum observed plasma concentration of a drug in a subject to whom the drug has been administered.

As used herein, the term "binding" refers to persistent contact, or adherence (however brief or intermittent), between two compounds.

As used herein, the terms "affinity", "binding affinity", and related terms refer to the strength and specificity of binding, such as binding between a ligand and its receptor. "Higher affinity" is used with reference to comparative binding between two ligands to a receptor, where the ligand which binds with higher affinity binds at a lower concentration than does the "lower affinity" ligand. For example, in a competitive binding experiment, a high affinity ligand will compete with a reference ligand for binding to a receptor at a lower concentration than will the low affinity ligand compete for binding at the receptor.

The term "specific binding" refers to binding that is more selective, and typically stronger, than mere non-specific adhesion between compounds. Specific binding may be exemplified by the binding which occurs between a ligand and its receptor.

Description of compounds useful in the methods disclosed herein, and suitable for the pharmaceutical compositions disclosed herein are described in accordance with principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, or physiological conditions.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., —$CH_2O$— is equivalent to —$OCH_2$—.

"Alkyl" refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons, such as $C_{1-2}$, $C_{1-3}$, $C_{1-4}$, $C_{1-5}$, $C_{1-6}$, $C_{1-7}$, $C_{1-8}$, $C_{1-9}$, $C_{1-10}$, $C_{2-3}$, $C_{2-4}$, $C_{2-5}$, $C_{2-6}$, $C_{3-4}$, $C_{3-5}$, $C_{3-6}$, $C_{4-5}$, $C_{4-6}$ and $C_{5-6}$. For example, $C_{1-6}$ alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.butyl, tert.butyl, pentyl, isopentyl, hexyl, etc.

"Alkoxy" refers to an alkyl group having an oxygen atom that connects the alkyl group to the point of attachment: alkyl-O—. As for the alkyl group, alkoxy groups can have any suitable number of carbon atoms, such as $C_{1-6}$. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, 2-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, etc.

"Halogen" refers to fluorine, chlorine, bromine and iodine.

"Haloalkyl" refers to alkyl, as defined above, where some or all of the hydrogen atoms are replaced with halogen atoms. As for the alkyl group, haloalkyl groups can have any suitable number of carbon atoms, such as $C_{1-6}$. For example, haloalkyl includes trifluoromethyl, fluoromethyl, etc. In some instances, the term "perfluoro" can be used to define a compound or radical where all the hydrogens are replaced with fluorine. For example, perfluoromethane includes 1,1,1-trifluoromethyl.

"Haloalkoxy" refers to an alkoxy group where some or all of the hydrogen atoms are substituted with halogen atoms. As for the alkyl group, haloalkoxy groups can have any suitable number of carbon atoms, such as $C_{1-6}$. The alkoxy groups can be substituted with 1, 2, 3, or more halogens. When all the hydrogens are replaced with a halogen, for example by fluorine, the compounds are per-substituted, for example, perfluorinated. Haloalkoxy includes, but is not limited to, trifluoromethoxy, 2,2,2,-trifluoroethoxy, perfluoroethoxy, etc.

"Cycloalkyl" refers to a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Cycloalkyl can include any number of carbons, such as $C_{3-6}$, $C_{4-6}$, $C_{5-6}$, $C_{3-8}$, $C_{4-8}$, $C_{5-8}$, $C_{6-8}$, $C_{3-9}$, $C_{3-10}$, $C_{3-11}$, and $C_{3-12}$. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic cycloalkyl rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene and adamantane. Cycloalkyl groups can also be partially unsaturated, having one or more double or triple bonds in the ring. Representative cycloalkyl groups that are partially unsaturated include, but are not limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene. When cycloalkyl is a saturated monocyclic $C_{3-8}$ cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. When cycloalkyl is a saturated monocyclic $C_{3-6}$ cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

"Heterocycloalkyl" refers to a saturated ring system having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O and S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can also be oxidized, such as, but not limited to, —S(O)— and —$S(O)_2$—. Heterocycloalkyl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. The heterocycloalkyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxalidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. The heterocycloalkyl groups can also be fused to aromatic or non-aromatic ring systems to form members including, but not limited to, indoline.

When heterocycloalkyl includes 3 to 8 ring members and 1 to 3 heteroatoms, representative members include, but are not limited to, pyrrolidine, piperidine, tetrahydrofuran, oxane, tetrahydrothiophene, thiane, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, morpholine, thiomorpholine, dioxane and dithiane. Heterocycloalkyl can also form a ring having 5 to 6 ring members and 1 to 2 heteroatoms, with representative members including, but not limited to, pyrrolidine, piperidine, tetrahydrofuran, tetrahydrothiophene, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, and morpholine.

"Aryl" refers to an aromatic ring system having any suitable number of ring atoms and any suitable number of rings. Aryl groups can include any suitable number of ring atoms, such as, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 ring atoms, as well as from 6 to 10, 6 to 12, or 6 to 14 ring members. Aryl groups can be monocyclic, fused to form bicyclic or tricyclic groups, or linked by a bond to form a biaryl group. Representative aryl groups include phenyl, naphthyl and biphenyl. Other aryl groups include benzyl, having a methylene linking group. Some aryl groups have from 6 to 12 ring members, such as phenyl, naphthyl or biphenyl. Other aryl groups have from 6 to 10 ring members, such as phenyl or naphthyl. Some other aryl groups have 6 ring members, such as phenyl. Aryl groups can be substituted or unsubstituted.

"Heteroaryl" refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O or S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can also be oxidized, such as, but not limited to, N-oxide, —S(O)— and —$S(O)_2$—. Heteroaryl groups can include any number of ring atoms, such as, 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. Heteroaryl groups can have from 5 to 8 ring members and from 1 to 4 heteroatoms, or from 5 to 8 ring members and from 1 to 3 heteroatoms, or from 5 to 6 ring members and from 1 to 4 heteroatoms, or from 5 to 6 ring members and from 1 to 3 heteroatoms. The heteroaryl group can include groups such as pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. The heteroaryl groups can also be fused to aromatic ring systems, such as a phenyl ring, to form members including, but not limited to, benzopyrroles such as indole and isoindole, benzopyridines such as quinoline and isoquinoline, benzopyrazine (quinoxaline), benzopyrimidine (quinazoline), benzopyridazines such as phthalazine and cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include heteroaryl rings linked by a bond, such as bipyridine. Heteroaryl groups can be substituted or unsubstituted.

The heteroaryl groups can be linked via any position on the ring. For example, pyrrole includes 1-, 2- and 3-pyrrole, pyridine includes 2-, 3- and 4-pyridine, imidazole includes 1-, 2-, 4- and 5-imidazole, pyrazole includes 1-, 3-, 4- and 5-pyrazole, triazole includes 1-, 4- and 5-triazole, tetrazole includes 1- and 5-tetrazole, pyrimidine includes 2-, 4-, 5- and 6-pyrimidine, pyridazine includes 3- and 4-pyridazine, 1,2,3-triazine includes 4- and 5-triazine, 1,2,4-triazine includes 3-, 5- and 6-triazine, 1,3,5-triazine includes 2-triazine, thiophene includes 2- and 3-thiophene, furan includes

2- and 3-furan, thiazole includes 2-, 4- and 5-thiazole, isothiazole includes 3-, 4- and 5-isothiazole, oxazole includes 2-, 4- and 5-oxazole, isoxazole includes 3-, 4- and 5-isoxazole, indole includes 1-, 2- and 3-indole, isoindole includes 1- and 2-isoindole, quinoline includes 2-, 3- and 4-quinoline, isoquinoline includes 1-, 3- and 4-isoquinoline, quinazoline includes 2- and 4-quinoazoline, cinnoline includes 3- and 4-cinnoline, benzothiophene includes 2- and 3-benzothiophene, and benzofuran includes 2- and 3-benzofuran.

Some heteroaryl groups include those having from 5 to 10 ring members and from 1 to 3 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include those having from 5 to 8 ring members and from 1 to 3 heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. Some other heteroaryl groups include those having from 9 to 12 ring members and from 1 to 3 heteroatoms, such as indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, benzofuran and bipyridine. Still other heteroaryl groups include those having from 5 to 6 ring members and from 1 to 2 ring heteroatoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, pyrazine, pyrimidine, pyridazine, thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole.

Some heteroaryl groups include from 5 to 10 ring members and only nitrogen heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, and cinnoline. Other heteroaryl groups include from 5 to 10 ring members and only oxygen heteroatoms, such as furan and benzofuran. Some other heteroaryl groups include from 5 to 10 ring members and only sulfur heteroatoms, such as thiophene and benzothiophene. Still other heteroaryl groups include from 5 to 10 ring members and at least two heteroatoms, such as imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiazole, isothiazole, oxazole, isoxazole, quinoxaline, quinazoline, phthalazine, and cinnoline.

"Heteroatoms" refers to O, S or N.

"Salt" refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of pharmaceutically acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

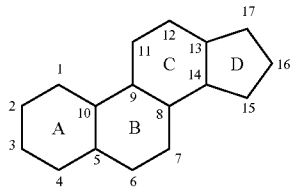
"Isomers" refers to compounds with the same chemical formula but which are structurally distinguishable.

"Tautomer" refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one form to another.

As used herein, the term "ketoconazole" refers to the molecule having the chemical name "1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]piperaziner)"; it is sold for clinical use under the name "Nizoral®", and may also be referred to by the abbreviation "keto".

As used herein, the terms "steroid" and "steroids", and the phrase "steroidal backbone" in the context of glucocorticoid receptor antagonists containing such refers to glucocorticoid receptor antagonists that contain modifications of the basic structure of cortisol, an endogenous steroidal glucocorticoid receptor ligand. The basic structure of a steroidal backbone is provided as Formula I:

Formula I

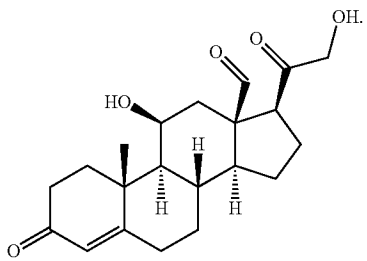



Steroidal Backbone

The two most commonly known classes of structural modifications of the cortisol steroid backbone to create glucocorticoid antagonists include modifications of the 11-β hydroxy group and modification of the 17-β side chain (See, e. g., Lefebvre (1989) J. Steroid Biochem. 33: 557-563).

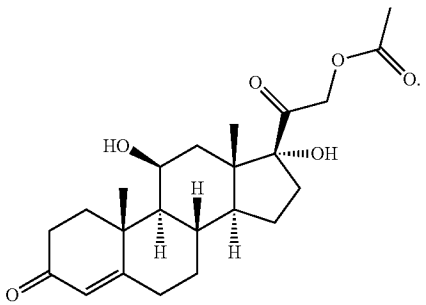
As used herein, the terms "progesterone receptor" and "PR" refer to a naturally occurring receptor which binds progesterone.

The term "aldosterone" refers to the naturally occurring mineralocorticoid hormone having the structure:




A mineralocorticoid receptor (MR), also known as a type I glucocorticoid receptor (GR I), is activated by aldosterone in humans.

The term "cortisol" refers to the naturally occurring glucocorticoid hormone (also known as hydrocortisone) having the structure:



As used herein, the term glucocorticoid receptor (GR) refers to a receptor that binds a glucocorticoid, such as cortisol, dexamethasone, or other molecules. A glucocorticoid receptor, also known as a corticosteroid receptor or as a type II glucocorticoid receptor (GR II), and in humans, as a cortisol receptor, is activated by cortisol in humans (or, e.g., by corticosterone ("cortisone") in some other animals, such as rats and mice). The human cortisol receptor (GR II receptor, Genbank: P04150) specifically binds to cortisol and/or cortisol analogs (e.g. dexamethasone). The term includes isoforms of GR II, recombinant GRII, and mutated GRII.

As used herein, the term glucocorticoid receptor modulator (GRM) refers to an agent that affects the action of a glucocorticoid receptor (GR). Such modulation may include activation (agonist action), partial activation (partial agonist action), inhibition (reduction in activation of the receptor under conditions where it would otherwise be activated, such as in the presence of cortisol), and blockade (complete or near complete suppression of activation of the receptor under conditions where it would otherwise be activated, such as in the presence of cortisol). GRMs may affect the activity of a GR by increasing or by decreasing the activity of the GR. GRMs include steroids, and, in embodiments, include pyrimidinediones; azadecalins; fused-ring azadecalins; heteroaryl-ketone fused-ring azadecalins; and other compounds.

As used herein, the terms "glucocorticoid agonist", "glucocorticoid receptor agonist", "glucocorticoid receptor type II agonist", and "GRII agonist" refer to a compound or agent which may bind to and activate a cortisol receptor. Such agents include, for example, cortisol, dexamethosone, prednisone, and other compounds and agents which bind to and activate a GRII.

As used herein, the terms "glucocorticoid antagonist", "glucocorticoid receptor antagonist", "glucocorticoid antagonist", "glucocorticoid receptor type II antagonist", "GRIT antagonist", and "GRA" refer to agents that inhibit the action of a cortisol receptor; such inhibition may include interfering with the binding of a glucocorticoid agonist such as cortisol, dexamethosone, or other compound or agent which may bind to and activate a cortisol receptor. A GRA is a glucocorticoid receptor modulator. Inhibition constants ($K_i$) for GRAs against the human cortisol receptor may be between about 0.0001 nM and about 1,000 nM; preferably may be between about 0.0005 nM and about 10 nM, and most preferably between about 0.001 nM and about 1 nM.

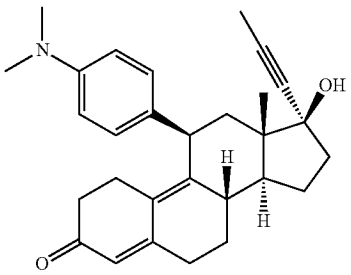
The term "glucocorticoid receptor antagonist" refers to any composition or compound which partially or completely inhibits (antagonizes) the binding of a glucocorticoid receptor (GR) agonist, such as cortisol, or cortisol analogs, synthetic or natural, to a GR. A "specific glucocorticoid receptor antagonist" refers to any composition or compound which inhibits any biological response associated with the binding of a GR to an agonist. By "specific," we intend the drug to preferentially bind to the GR rather than another nuclear receptors, such as mineralocorticoid receptor (MR) or progesterone receptor (PR).

By "specific," the drug preferentially binds to the GR rather than other nuclear receptors, such as mineralocorticoid receptor (MR), androgen receptor (AR), or progesterone receptor (PR). It is preferred that the specific glucocorticoid receptor antagonist bind GR with an affinity that is 10× greater ($1/10^{th}$ the $K_d$ value) than its affinity to the MR, AR, or PR. In a more preferred embodiment, the specific glucocorticoid receptor antagonist binds GR with an affinity that is 100× greater ($1/100^{th}$ the $K_d$ value) than its affinity to the MR, AR, or PR.

In embodiments, a glucocorticoid receptor modulator (GRM) is a glucocorticoid receptor antagonist (GRA). In embodiments, the GRA is an antagonist of a glucocorticoid type II (GRIT) receptor. In embodiments, the GRA binds preferentially to a GRII receptor as compared to its binding to a glucocorticoid type I (GRI) receptor. In embodiments, the GRA reduces the activation of a GRIT receptor. In embodiments, the GRA reduces the activity of a GRII receptor. In embodiments, the GRA may bind to a progesterone receptor (PR), and may bind to a glucocorticoid receptor with higher affinity than it binds to PR. In embodiments, the GRA is mifepristone. In embodiments, the GRA is a selective inhibitor of the glucocorticoid receptor. In embodiments, the GRA may only poorly bind to PR, or may not measurably bind to PR.

As used herein, a "steroidal glucocorticoid receptor antagonist" means a molecule including a steroid backbone structure which antagonizes the binding of cortisol, corticosterone, or dexamethasone to a glucocorticoid receptor, or which reduces or blocks the activation of a glucocorticoid receptor by cortisol, corticosterone, or dexamethasone. Examples of steroidal glucocorticoid receptor antagonists include mifepristone, monodemethylated mifepristone, didemethylated mifepristone, 17-α-[3'-hydroxy-propynyl] mifepristone, ulipristal (CDB-2914), CDB-3877, CDB-3963, CDB-3236, CDB-4183, cortexolone, dexamethasone-oxetanone, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11(-(4-dimethylaminoethoxyphenyl)-17(-propynyl-17(-hydroxy-4,9-estradien-3-one, and 17(-hydroxy-17(-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one.

Mifepristone is a GRA, which binds to GRII (and which also binds to a progesterone receptor). As used herein, the term "mifepristone" refers to 11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(1-propynyl)-estra-4,9-dien-3-one), also referred to as RU486, or as RU38.486, or as 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one). Mifepristone binds to the glucocorticoid receptor (GR), typically with high affinity, and inhibits the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to a GR receptor. Salts, hydrates and prodrugs of mifepristone are all included in the term "mifepristone" as used herein. Thus, used herein, "mifepristone" refers to the molecule that has the following structure:




and to salts, hydrates and prodrugs thereof, and pharmaceutical compositions thereof. Mifepristone is also sometimes abbreviated as "mife" and "MIFE".

Metabolites of mifepristone include RU42633 (desmethylmifepristone: (8S,11R,13S,14S,17S)-17-hydroxy-13-

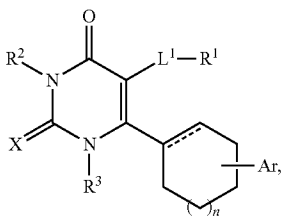
methyl-11-[4-(methylamino)phenyl]-17-prop-1-ynyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one); RU42698 (22-hydroxy mifepristone: (8S,11R,13S,14S,17S)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(3-hydroxyprop-1-ynyl)-13-methyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one); and RU42848 (didesmethylmifepristone: (8S,11R,13S,14S,17S)-11-(4-aminophenyl)-17-hydroxy-13-methyl-17-prop-1-ynyl-1,2,6,7,8,11,12,14,15,16-decahydrocyclopenta[a]phenanthren-3-one), among others.

In some embodiments, the GRA comprises a steroidal backbone with at least one phenyl-containing moiety in the 11-β position of the steroidal backbone. In some cases, the phenyl-containing moiety in the 11-β position of the steroidal backbone is a dimethylaminophenyl moiety. In some cases, the GRA is mifepristone. In some embodiments, the GRA is selected from the group consisting of 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9 estradien-3-one and (17α)-17-hydroxy-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one. In some embodiments, the GRA is (11β, 17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one.

As used herein, the phrase "non-steroidal backbone" in the context of glucocorticoid receptor antagonists containing such refers to glucocorticoid receptor antagonists that do not share structural homology to, or are not modifications of, cortisol. Such compounds include, for example, small molecules, synthetic mimetics and analogs of proteins, including partially peptidic, pseudopeptidic and non-peptidic molecular entities.

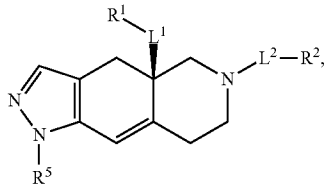
In some embodiments, the GRA is a non-steroidal compound. In embodiments, non-steroidal GRA compounds include compounds having a cyclohexyl-pyrimidine backbone; non-steroidal GRA compounds having a fused azadecalin backbone; non-steroidal GRA compounds having a heteroaryl ketone fused azadecalin backbone; and non-steroidal GRA compounds having an octahydro fused azadecalin backbone. Exemplary glucocorticoid receptor antagonists having a cyclohexyl-pyrimidine backbone include those described in U.S. Pat. No. 8,685,973. Exemplary glucocorticoid receptor antagonists having a fused azadecalin backbone include those described in U.S. Pat. Nos. 7,928,237; and 8,461,172. Exemplary glucocorticoid receptor antagonists having a heteroaryl ketone fused azadecalin backbone include those described in U.S. Pat. No. 8,859,774. Exemplary glucocorticoid receptor antagonists having an octohydro fused azadecalin backbone include those described in U.S. Patent Application Publication 20150148341.

In some cases, the GRA having a non-steroidal backbone is a cyclohexyl pyrimidine. In some cases, wherein the cyclohexyl pyrimidine has the following formula:

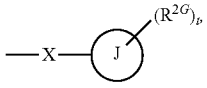


wherein the dashed line is absent or a bond; X is selected from the group consisting of O and S; $R^1$ is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, optionally substituted with from 1 to 3 $R^{1a}$ groups; each $R^{1a}$ is independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl $OR^{1b}$, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloaloxy, $OR^{1b}$, $NR^{1b}R^{1c}$, $C(O)R^{1b}$, $C(O)OR^{1b}$, $OC(O)R^{1b}$, $C(O)NR^{1b}R^{1c}$, $NR^{1b}C(O)R^{1c}$, $SO_2R^{1b}$, $SO_2NR^{1b}R^{1c}$, cycloalkyl, heterocycloalkyl, aryl and heteroaryl; $R^{1b}$ and $R^{1c}$ are each independently selected from the group consisting of H and $C_{1-6}$ alkyl; $R^2$ is selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{1-6}$ alkyl-$OR^{1b}$, $C_{1-6}$ alkyl $NR^{1b}R^{1c}$ and $C_{1-6}$ alkylene heterocycloalkyl; $R^3$ is selected from the group consisting of H and $C_{1-6}$ alkyl; Ar is aryl, optionally substituted with 1-4 $R^4$ groups; each $R^4$ is independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $C_{1-6}$ haloalkyl and $C_{1-6}$ haloalkoxy; $L^1$ is a bond or $C_{1-6}$ alkylene; and subscript n is an integer from 0 to 3, or salts and isomers thereof.

In some cases, the GRA having a non-steroidal backbone is a fused azadecalin. In some cases, the fused azadecalin is a compound having the following formula:

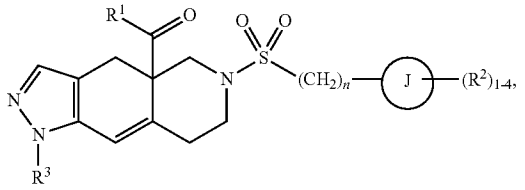


wherein $L^1$ and $L^2$ are members independently selected from a bond and unsubstituted alkylene; $R^1$ is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, —$OR^{1A}$, $NR^{1C}R^{1D}$, —$C(O)NR^{1C}R^{1D}$, and —$C(O)OR^{1A}$, wherein $R^{1A}$ is a member selected from hydrogen, unsubstituted alkyl and unsubstituted heteroalkyl, $R^{1C}$ and $R^{1D}$ are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl, wherein $R^{1C}$ and $R^{1D}$ are optionally joined to form an unsubstituted ring with the nitrogen to which they are attached, wherein said ring optionally comprises an additional ring nitrogen; $R^2$ has the formula:



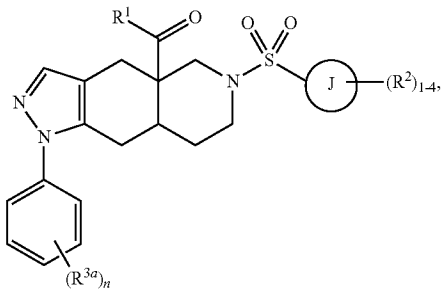
wherein $R^{2G}$ is a member selected from hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, —CN, and —$CF_3$; J is phenyl; t is an integer from 0 to 5; X is —$S(O_2)$—; and $R^5$ is phenyl optionally substituted with 1-5 $R^{5A}$ groups, wherein $R^{5A}$ is a member selected from hydrogen, halogen, —$OR^{5A1}$, $S(O_2)NR^{5A2}R^{5A3}$, —CN, and unsubstituted alkyl, wherein $R^{5A1}$ is a member selected from hydrogen and unsubstituted alkyl, and $R^{5A2}$ and $R^{5A3}$ are members independently selected from hydrogen and unsubstituted alkyl, or salts and isomers thereof.

In some cases, the GRA having a non-steroidal backbone is a heteroaryl ketone fused azadecalin or an octahydro fused azadecalin. In some cases, the heteroaryl ketone fused azadecalin has the formula:



wherein $R^1$ is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from $R^{1a}$; each $R^{1a}$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, CN, N-oxide, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl; ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S; each $R^2$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, $C_{1-6}$ alkyl-$C_{1-6}$ alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, $SR^{2a}$, $S(O)R^{2a}$, $S(O)_2R^{2a}$, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 $R^{2c}$ groups; alternatively, two $R^2$ groups linked to the same carbon are combined to form an oxo group (=O); alternatively, two $R^2$ groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 $R^{2d}$ groups; $R^{2a}$ and $R^{2b}$ are each independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl; each $R^{2c}$ is independently selected from the group consisting of hydrogen, halogen, hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, CN, and $NR^{2a}R^{2b}$; each $R^{2d}$ is independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl, or two $R^{2d}$ groups attached to the same ring atom are combined to form (=O); $R^3$ is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 $R^{3a}$ groups; each $R^{3a}$ is independently selected from the group consisting of hydrogen, halogen, and $C_{1-6}$ haloalkyl; and subscript n is an integer from 0 to 3; or salts and isomers thereof.

In some cases, the octahydro fused azadecalin has the formula:



wherein $R^1$ is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from $R^{1a}$; each $R^{1a}$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, N-oxide, and $C_{3-8}$ cycloalkyl; ring J is selected from the group consisting of an aryl ring and a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S; each $R^2$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, $C_{1-6}$ alkyl-$C_{1-6}$alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, $SR^{2a}$, $S(O)R^{2a}$, $S(O)_2R^{2a}$, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl having from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S; alternatively, two $R^2$ groups on adjacent ring atoms are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 $R^{2c}$ groups; $R^{2a}$, $R^{2b}$ and $R^{2c}$ are each independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl; each $R^{3a}$ is independently halogen; and subscript n is an integer from 0 to 3, or salts and isomers thereof.

Further examples of non-steroidal glucocorticoid receptor antagonists include, for example N-(2-[4,4',441-trichlorotrityl]oxyethyl)morpholine; 1-(2[4,4',4"-trichlorotrityl]oxyethyl)-4-(2-hydroxyethyl)piperazine dimaleate; N-([4,4',4"]-trichlorotrityl)imidazole; 9-(3-mercapto-1,2,4-triazolyl)-9-phenyl-2,7-difluorofluorenone; 1-(2-chlorotrityl)-3,5-dimethylpyrazole; 4-(morpholinomethyl)-A-(2-pyridyl)benzhydrol; 5-(5-methoxy-2-(N-methylcarbamoyl)-phenyl)dibenzosuberol; N-(2-chlorotrityl)-L-prolinol acetate; 1-(2-chlorotrityl)-1,2,4-triazole; 1,S-bis(4,4',4"-trichlorotrityl)-1,2,4-triazole-3-thiol; 4α(S)-Benzyl-2(R)-chloroethynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol ("CP 394531"), 4α(S)-Benzyl-2(R)-prop-1-ynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol ("CP-409069"), trans-(1R,2R)-3,4-dichloro-N-methyl-N-[2-1 pyrrolidinyl)cyclohexyl] benzeneacetamide, bremazocine, and ethylketocyclazocine.

As used herein, the term "hormone-sensitive cancer" refers to any cancer which may be affected by a hormone; hormones typically increase proliferation of hormone-sensitive cancers. Hormone sensitive cancers include, e.g., prostate cancer and other androgen-sensitive cancers; breast cancer, ovarian cancer and other estrogen-sensitive or progesterone-sensitive cancers.

As used herein, the term "chemotherapy" refers to medical treatments typically used to treat cancer. Chemotherapy treatments include the use of agents which are toxic to cancerous tissues and cells, or which act to slow or reduce the growth or spread of cancerous tissues and cells. Chemotherapy agents include antineoplastic agents and may be derived from natural compounds (e.g., taxols); may be, may mimic, or may reduce or block the actions of naturally occurring hormones, growth factors, or immunologically active molecules; may be synthetic small molecules; may be antibodies or antibody conjugates; and may be other agents. Exemplary chemotherapy agents include, but are not limited to, taxanes, taxol, docetaxel, paclitaxel, actinomycin, anthracyclines, doxorubicin, daunorubicin, valrubicin, bleomycin, cisplatin, trastuzumab (Herceptin®), trastuzumab emtasine (Kadcyla®), imatinib (Gleevec®), eribulin (Halaven®), among others known in the art.

As used herein, a phrase of the form "the reduced dose of Z is a dose that is at least about X % less than the original

dose" (where "Z" represents a pharmaceutical compound or pharmaceutical composition, and "X" represents a numerical value) is used to indicate that the reduced dose is an amount of Z calculated by 1) multiplying the amount of Z in the original dose by X % to obtain a multiplicative product, and 2) subtracting that product from the original dose. Thus, for example, where the original dose is 600 mg, and X % is 50%, the multiplicative product of 600 mg and 50% is 300 mg, and the reduced dose is 300 mg; and, for example, where the original dose is 900 mg, and X % is 66%, the multiplicative product of 900 mg and 66% is about 600 mg (594 mg), and the reduced dose is about 300 mg (306 mg).

As used herein, the terms "pharmaceutical composition" and "formulation" refer to compositions suitable for administration to a patient for treatment of a medical condition or for amelioration of symptoms of a medical condition. A pharmaceutical composition as disclosed herein includes an active ingredient (e.g., a GRA, such as, e.g., mifepristone; or a combination of a GRA and a SI, where the SI may be, e.g., ketoconazole) and a pharmaceutically acceptable excipient. In embodiments, a pharmaceutical composition includes one or more active ingredients and one or more pharmaceutically acceptable excipients.

As used herein, the terms "pharmaceutically acceptable excipient" and "pharmaceutically acceptable carrier" refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors, and the like. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

As used herein, the terms "sustained release," "slow release," "long acting," "prolonged release," and the like refer to a pharmaceutical composition or formulation containing at least one active ingredient (e.g., GRA, SI, or combination thereof) formulated to maintain a therapeutic concentration of active ingredient(s) in a patient for a longer period of time in comparison to formulations that are not designed for such sustained release. In some cases, the sustained release formulation maintains therapeutic concentration of one or more active ingredient(s) for, or for at least, one week, two weeks, three weeks, four weeks, five weeks, or six weeks. In some cases, the sustained release formulation is administered to a patient every one, two, three, four, five, or six weeks.

As used herein, a "steroidogenesis inhibitor" is a compound which reduces or blocks the synthesis of steroid molecules when administered to an animal, or subject, which normally produces steroids. Steroidogenesis inhibitors include, for example, ketoconazole, metyrapone, etomidate, and other drugs. A steroidogenesis inhibitor may act by one or more of several mechanisms, including, e.g., blocking synthesis of steroid molecules (e.g., ketoconazole, metyrapone).

As used herein, the term "CYP enzyme" refers to a cytochrome P450 enzyme. Cytochrome P450 enzymes are important in many metabolic and catabolic reactions in humans and other animals, and play important roles in drug metabolism and action. Drug-drug interactions in which administration of one drug affects the concentration, half-life, activity, or other effect of another drug may include effects on CYP enzymes by induction of CYP enzymes (increasing the amount or activity of one or more CYP enzymes); inhibition (reducing the activity of one or more CYP enzymes); competition (competing for sites or occupying sites, e.g., as a substrate, of one or more CYP enzymes); or by other means. Particular CYP enzymes include, for example, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A enzymes.

As used herein, a "CYP3A inhibitor" is a compound which reduces or blocks the activity of the cytochrome CYP3A, or reduces or blocks the expression of the gene-product of CYP3A genes (e.g., inhibits transcription or translation of CYP3A genes). CYP3A inhibitors may be termed strong or moderate if their administration, along with a test drug known to be metabolized by CYP3A enzymes (such as, e.g., midazolam), raises the AUC (area under the concentration curve) of the test drug by greater than five-fold (strong CYP3A inhibitors) or by between two-fold and five-fold (moderate CYP3A inhibitors). Inhibitors of CYP3A include, for example, ketoconazole, itraconazole, fluconazole, cimetidine, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir, fosamprenavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole.

Strong CYP3A inhibitors include, for example, ketoconazole, itraconazole, nefazodone, ritonavir, nelfinavir, indinavir, atazanavir, amprenavir and fosamprenavir, clarithromycin, conivaptan, lopinavir/ritonavir, posaconazole, saquinavir, telithromycin, and voriconazole.

Metyrapone (also known as Metopirone®) is 2-methyl-1,2-bis-(3-pyridyl)-1-propanone. Metopirone is believed to reduce cortisol and corticosterone production by inhibiting the 11-β-hydroxylation reaction in the adrenal cortex.

Etomidate (also known as Amidate®) is R-(+)-ethyl-1-(1-phenylethyl)-1H-imidazole-5-carboxylate. Although primarily used as a rapid-onset anesthetic, etomidate also lowers plasma cortisol levels. It is believed to reduce corticosteroid synthesis in the adrenal cortex by inhibiting 11β-hydroxylase.

Ketoconazole (1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-[(1H-imidazol-1-yl)-methyl]-1,3-dioxolan-4-yl]methoxy] phenyl]piperazine) is often used to treat fungal infections (e.g., (NIZORAL®) for the treatment of fungal infections). In addition, ketoconazole is a steroidogenesis inhibitor and can reduce the production of steroid molecules (such as, e.g., steroid hormones), typically by blocking the metabolism of cholesterol. Ketoconazole thus may be used to treat excessive cortisol production (e.g., to treat Cushing's disease and Cushing's syndrome), to reduce androgen production (e.g., in patients with hormone-sensitive cancers such as prostate cancer), to reduce estrogen or progesterone production (e.g., in patients with hormone-sensitive cancers such as breast cancer), and other treatments.

However, ketoconazole often has serious deleterious effects on liver and other organs. Thus, it is desirable to minimize the dose of ketoconazole administered to a patient, and methods for reducing the dose of ketoconazole are desired.

Treatment Methods

Methods disclosed herein include methods of treating a disease characterized by excess steroid levels, or by excess activity due to steroids. Methods disclosed herein also include methods of treating a disease that may be treated by reducing or blocking the action of steroids, such as steroid hormones. In embodiments, the disease is characterized by excess cortisol levels, such as, e.g., Cushing's syndrome, and in particular, Cushing's Disease. (As noted above, both Cushing's syndrome and Cushing's Disease are character-

ized by excess cortisol; Cushing's Disease falls within the definition of Cushing's syndrome as a particular type or example of Cushing's syndrome; thus, all discussion and disclosure regarding Cushing's syndrome includes Cushing's Disease.) Methods disclosed herein also include methods of treating cancer and cancerous tumors, such as hormone-sensitive cancers including prostate cancer, comprising concomitant administration of a GRM and ketoconazole to provide thereby beneficial therapeutic effects. Methods, compositions, and kits disclosed herein are related to the methods compositions, and kits and compositions disclosed in U.S. Provisional Patent Application Ser. No. 62/465,772, filed Mar. 1, 2017, and U.S. Provisional Patent Application Ser. No. 62/466,867, filed Mar. 3, 2017, which applications are hereby incorporated by reference in their entireties.

For example, the present methods include concomitantly administering to a patient a CYP3A inhibitor and a glucocorticoid receptor modulator (GRM), such as a glucocorticoid receptor antagonist (GRA). In embodiments, the CYP3A inhibitor is ketoconazole. In embodiments, the CYP3A inhibitor is ketoconazole and the GRA is mifepristone. In embodiments, the patient is receiving a CYP3A inhibitor (such as, e.g., ketoconazole) and is concomitantly administered an amount of a GRA (such as, e.g., mifepristone) effective to treat Cushing's syndrome, e.g., effective to control hyperglycemia secondary to hypercortisolism in an adult patient suffering from endogenous Cushing's syndrome. In embodiments, the adult patient suffering from endogenous Cushing's syndrome has type 2 diabetes mellitis or glucose intolerance. In embodiments, the adult patient suffering from endogenous Cushing's syndrome has failed surgery or is not a candidate for surgery (e.g., referring to surgical treatment for Cushing's syndrome). In embodiments, the adult patient suffering from endogenous Cushing's syndrome has type 2 diabetes mellitis or glucose intolerance and has failed surgery or is not a candidate for surgery (e.g., referring to surgical treatment for Cushing's syndrome).

In embodiments, the present methods include methods for treating Cushing's syndrome in a patient taking a GRA, comprising reducing the daily dosage amount of the GRA from an original GRA dose to an adjusted GRA dose when the patient is receiving concomitant administration of a CYP3A inhibitor. In embodiments, the adjusted dose of GRA is at least 25% less than the original dose. In embodiments, the adjusted dose of GRA is at least 33% less than the original dose. In embodiments, the adjusted dose of GRA is less than the original dose by a fraction of the original dose selected from 10%, 20%, 25%, 30%, 33%, $33^{1/3}$%, and 50%. In embodiments, the GRA is mifepristone, and the adjusted mifepristone dose is selected from 300 mg per day, 600 mg per day, and 900 mg per day. In embodiments, the CYP3A inhibitor is ketoconazole. In embodiments, the CYP3A inhibitor is ketoconazole and the GRA is mifepristone. In embodiments, the patient is receiving a CYP3A inhibitor (such as, e.g., ketoconazole) and is concomitantly administered an amount of a GRA (such as, e.g., mifepristone) effective to treat Cushing's syndrome, e.g., effective to control hyperglycemia secondary to hypercortisolism in an adult patient suffering from endogenous Cushing's syndrome. In embodiments, the adult patient suffering from endogenous Cushing's syndrome has type 2 diabetes mellitis or glucose intolerance. In embodiments, the adult patient suffering from endogenous Cushing's syndrome has failed surgery or is not a candidate for surgery (e.g., referring to surgical treatment for Cushing's syndrome). In embodiments, the adult patient suffering from endogenous Cushing's syndrome has type 2 diabetes mellitis or glucose intolerance and has failed surgery or is not a candidate for surgery (e.g., referring to surgical treatment for Cushing's syndrome).

For example, the present disclosed methods include administering to a patient receiving ketoconazole an effective amount of a glucocorticoid receptor modulator (GRM), such as a glucocorticoid receptor antagonist (GRA). In embodiments, the patient is receiving ketoconazole. In embodiments, the patient is receiving ketoconazole and the GRA is mifepristone. In embodiments, the patient is receiving ketoconazole and is administered an amount of mifepristone effective to reduce the effect of a steroid such as cortisol in the patient.

Thus, in embodiments, the methods disclosed herein include a method for treating a patient who is receiving ketoconazole treatment for excess steroid levels, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering a GRA to the patient receiving ketoconazole, whereby the patient receiving ketoconazole is administered a GRA for treating excess steroid levels. In embodiments, the GRA is mifepristone. In embodiments, the disease is Cushing's syndrome. In embodiments, the disease is Cushing's Disease.

Thus, in embodiments, the methods disclosed herein include a method for treating a patient who is receiving ketoconazole treatment to reduce or block the effects of steroids, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering a GRA to the patient receiving ketoconazole, whereby the patient receiving ketoconazole is administered a GRA for treating the effects of steroids in the patient. In embodiments, the GRA is mifepristone. In embodiments, the effects of steroids include hypercortisolemic effects, such as the effects of Cushing's syndrome. In embodiments, the effects of steroids include hormonal effects, such as effects on hormone-sensitive cancer.

Applicant further discloses a method for treating a Cushing's syndrome patient who is receiving ketoconzole treatment, said ketoconzole treatment comprising administering an original dose of ketoconzole to said patient, said method comprising: administering a GRA to the patient receiving ketoconzole, wherein the amount of GRA administered is a first dose of GRA, whereby the patient receiving ketoconzole is administered a GRA for treating Cushing's syndrome. In embodiments, the GRA is mifepristone. In embodiments, the or Cushing's syndrome patient suffers from Cushing's Disease.

For example, the present disclosed methods include concomitantly administering to a patient in need thereof, a) an effective amount of a glucocorticoid receptor modulator (GRM), such as a glucocorticoid receptor antagonist (GRA), and b) an effective amount of ketoconazole, such as ketoconazole, thereby reducing the effect, the amount, or both, of steroids such as cortisol in the patient. For example, a Cushing's syndrome patient may be in need of reducing their blood levels of cortisol, or may be in need of reducing the effect of cortisol in the patient. For example, a cancer patient may be in need of reducing their blood levels of a steroid, such as an androgen, a progestogen, an estrogen, or other steroid.

Thus, in embodiments of the methods disclosed herein, a subject currently receiving ketoconazole is administered a GRM. In embodiments of the methods disclosed herein, a

subject currently receiving ketoconzole as treatment for a condition characterized by excess steroid levels, or as treatment of a condition that is treated by reducing steroid levels or by reducing steroid effects, is administered a GRM, whereby the subject is treated for that condition. In embodiments, the condition is characterized by excessive cortisol levels. In embodiments, the condition is Cushing's syndrome. In embodiments, the condition is a cancer characterized by the deleterious action of steroid hormones on cells, such as cancer cells; the cancer may be hormone-sensitive cancer that may be treated by lowering the levels of a steroid in the patient. In embodiments, the hormone sensitive cancer is prostate cancer, breast cancer, or ovarian cancer.

Accordingly, Applicant discloses herein a method for treating a patient in need of reduced steroid levels, the patient receiving an original dose of ketoconazole, said method comprising:

administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first GRA dose is administered concomitantly with said dose of ketoconazole, whereby the patient is administered both an original dose of ketoconazole and a first dose of a GRA for reducing steroid levels in the patient. In embodiments of such methods, wherein said first dose of GRA comprises an amount of the GRA that is effective to aid in reducing steroid levels in the patient without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by the original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity.

Accordingly, Applicant discloses herein a method for treating a patient suffering from excess steroid levels, the patient receiving an original dose of ketoconazole, said method comprising:

administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first GRA dose is administered concomitantly with said dose of ketoconazole, whereby the patient is administered both an original dose of ketoconazole and a first dose of a GRA for reducing steroid levels in the patient. In embodiments of such methods, wherein said first dose of GRA comprises an amount of the GRA that is effective to aid in reducing steroid levels in the patient without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by the original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity. In embodiments, the excess steroid comprises excess androgen. In embodiments, the excess steroid comprises excess progestogen. In embodiments, the excess steroid comprises excess estrogen. In embodiments, the excess steroid comprises excess cortisol.

Accordingly, in further embodiments, Applicant discloses herein methods for treating a Cushing's syndrome patient, the patient receiving an original dose of ketoconazole, said methods comprising:

administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first GRA dose is administered concomitantly with said dose of ketoconazole, whereby the patient is administered both an original dose of ketoconazole and a first dose of a GRA for treating Cushing's syndrome. In embodiments of such methods, wherein said first dose of GRA comprises an amount of the GRA that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by the original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity.

In embodiments, Applicant discloses methods for treating a Cushing's syndrome patient who is receiving ketoconazole treatment, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering said original dose of ketoconazole to said patient; and administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first dose of GRA comprises an amount of said GRA that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by the original dose of ketoconazole, whereby the patient is administered both ketoconazole and a GRA for treating Cushing's syndrome and is not exposed to increased risk of ketoconazole toxicity. In embodiments, said GRA is mifepristone. In embodiments, the original dose of ketoconazole and the first dose of GRA are administered within a short time of each other. In embodiments, the original dose of ketoconazole and the first dose of GRA are administered at substantially the same time. In embodiments, the original dose of ketoconazole and the first dose of GRA are administered concomitantly. In embodiments, the GRA is mifepristone.

Thus, in embodiments of these methods, administration of the ketoconazole and of the GRA comprises concomitant administration of the original dose of ketoconazole and the first dose of the GRA. In embodiments of concomitant administration, ketoconazole and the GRA are administered to the subject simultaneously. Such concomitant administration of a GRA may be by oral administration; by intravenous administration; subcutaneous administration; parenteral administration; intra-arterial administration; nasal administration; topical administration; or by other routes of administration, or combinations thereof.

In embodiments of the methods disclosed herein, ketoconazole and the GRA are administered to the patient in a single pill containing both the ketoconazole and the GRA, or are administered in a single liquid formulation containing both the ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

In embodiments of the methods disclosed herein, the first dose of the GRA is a dose selected from about 25 milligrams (mg), about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 900 mg, about 1000 mg, about 1200 mg, about 1500 mg, about 1800 mg, and about 2000 mg. In embodiments, the dose of the GRA is a dose of mifepristone selected from about 300 mg, about 600 mg, about 900 mg, about 1200 mg, and about 1500 mg.

The methods disclosed herein include repeated administration of a GRA to a patient in need of treatment, including repeated concomitant administration of ketoconazole and a GRA.

For example, in yet further embodiments, a second dose of GRA is administered, wherein said second dose is administered after the administration of the first dose of GRA. The second dose of GRA may comprise about the same amount of said GRA as the first dose of the GRA; may comprise a greater amount of said GRA than the first dose of GRA; or may comprise a smaller amount of GRA than the first dose of GRA. In embodiments of these methods, the GRA is mifepristone.

The methods disclosed herein may further comprise: administering a subsequent dose of ketoconazole and a second dose of GRA, wherein said subsequent dose and said second dose are both administered after the administration of the first dose of the GRA. In embodiments, the second dose of GRA comprises about the same amount of the GRA as the first dose of GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments, the subsequent dose of ketoconazole comprises a lesser amount of ketoconazole than the amount of the original dose of ketoconazole. In embodiments of these methods, the GRA is mifepristone.

In embodiments, the second dose of GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA. In embodiments, the second dose of GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments of these methods, the GRA is mifepristone.

In embodiments comprising repeated administration of a GRA to a patient in need of treatment, including repeated concomitant administration of ketoconazole and a GRA, ketoconazole and the GRA may be administered simultaneously. In embodiments of such methods, the GRA may be mifepristone.

In embodiments, ketoconazole and a GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

Further embodiments of the methods disclosed herein may include further steps, e.g., may comprise administration of a third dose of a GRA, wherein said third dose of the GRA is administered after the administration of the second dose of the GRA. In embodiments, such a third dose of GRA comprises about the same amount of the GRA as the second dose of the GRA. In embodiments, such a third dose of GRA comprises a greater amount of the GRA than the second dose of the GRA. In embodiments, such a third dose of GRA is administered after the administration of the second dose of the GRA. In embodiments, such a third dose of GRA comprises about the same amount of GRA as the amount of said second dose of the GRA. In embodiments, such a third dose of GRA comprises a lesser amount of the GRA than the amount of said second dose of the GRA. In embodiments, such a third dose of GRA comprises a greater amount of the GRA than the amount of said second dose of the GRA. In such embodiments, the GRA may be mifepristone.

In embodiments, methods disclosed herein comprise concomitant administration of ketoconazole and a third dose of GRA. In embodiments of such concomitant administration, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of such concomitant administration, ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

Embodiments of the methods disclosed herein comprise treatments for patients suffering from Cushing's syndrome; in embodiments, the Cushing's syndrome patient suffers from Cushing's Disease. Such treatments for Cushing's syndrome comprise concomitant administration of ketoconazole and a GRA to the patient.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with ketoconazole and with a glucocorticoid receptor antagonist (GRA). In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with ketoconazole and a GRA, wherein the dose of ketoconazole administered concomitantly with the GRA is not reduced with respect to the ketoconazole dose administered to the patient in the absence of concomitant treatment with ketoconazole and a GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with a GRA and ketoconazole. In embodiments, the GRA is mifepristone.

Applicant discloses herein methods for treating a Cushing's syndrome patient, the patient receiving an original dose of ketoconazole, said method comprising: administering a first dose of a glucocorticoid receptor antagonist (GRA) to the patient, wherein said first GRA dose is administered concomitantly with the dose of SI, whereby the patient is administered both an original dose of ketoconazole and a first dose of a GRA for treating Cushing's syndrome. In embodiments, the patient suffers from Cushing's Disease.

In embodiments, Applicant discloses herein methods for treating a Cushing's syndrome patient, the patient receiving an original dose of ketoconazole, the method comprising: administering a first dose of mifepristone to the patient, wherein the first mifepristone dose is administered concomitantly with the dose of ketoconazole, whereby the patient is administered both an original dose of ketoconazole and a first dose of mifepristone for treating Cushing's syndrome. In embodiments, the patient suffers from Cushing's Disease.

In further embodiments of such methods, wherein said first dose of a GRA comprises a GRA amount that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by said original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity. In embodiments, administration of ketoconazole and of the GRA comprises concomitant administration of the original dose of ketoconazole and the first dose of the GRA. In embodiments, administering a GRA comprises oral administration of the GRA. In embodiments, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments, ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

In embodiments of the methods disclosed herein, the first dose of the GRA is selected from about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 900 mg, about 1000 mg, about 1200 mg, about 1500 mg, about 1800 mg, about 2000 mg, about 2100 mg, about 2400 mg, about 2700 mg, and about 3000 mg. In embodiments of the methods disclosed herein, the first dose of the GRA is a dose of mifepristone selected from about 1500 mg mifepristone, about 1200 mg mifepristone, about 900 mg mifepristone, about 600 mg mifepristone, and about 300 mg mifepristone.

Further embodiments of the methods disclosed herein comprise administering a second dose of GRA, wherein said second dose is administered after the administration of the

first dose of GRA. In embodiments, the second dose of GRA comprises about the same amount of said GRA as the first dose of the GRA. In embodiments, the second dose of GRA comprises a greater amount of said GRA than the first dose of GRA. In embodiments, the GRA is mifepristone.

Further embodiments of the methods disclosed herein comprise administering a subsequent dose of ketoconazole and a second dose of GRA, wherein the subsequent ketoconazole dose and the second GRA dose are both administered after the administration of the first dose of the GRA. In embodiments, the second dose of GRA comprises about the same amount of the GRA as the first dose of the GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments, the subsequent dose of ketoconazole comprises a lesser amount of ketoconazole than the amount of the original dose of ketoconazole. In embodiments, the second dose of GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA. In embodiments, the second dose of GRA comprises a greater amount of the GRA than the amount of the first dose of the GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments, the GRA is mifepristone.

In embodiments, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments, the GRA is mifepristone. In embodiments, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments, ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments, ketoconazole and mifepristone are administered to the patient in a single pill containing both ketoconazole and mifepristone, or in a single liquid formulation containing both ketoconazole and mifepristone. In embodiments, ketoconazole and mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising both ketoconazole and mifepristone.

Embodiments of the methods disclosed herein further comprise administration of a third dose of GRA, wherein said third dose of the GRA is administered after the administration of the second dose of the GRA. In embodiments, the third dose of GRA comprises about the same amount of the GRA as the second dose of the GRA. In embodiments, the third dose of GRA comprises a greater amount of the GRA than the second dose of the GRA. In embodiments, the methods further comprise administration of a third dose of GRA, wherein the third dose of the GRA is administered after the administration of the second dose of the GRA. In embodiments, the third dose of GRA comprises about the same amount of GRA as the amount of said second dose of the GRA. In embodiments, the third dose of the GRA comprises a lesser amount of the GRA than the amount of said second dose of the GRA. In embodiments, the third dose of GRA comprises a greater amount of the GRA than the amount of said second dose of the GRA. In embodiments, administration of the third GRA dose comprises concomitant administration ketoconazole and the third dose of GRA. In such embodiments, ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of the methods comprising such third dose of GRA, ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation containing both ketoconazole and the GRA. In embodiments, the GRA is mifepristone.

Applicant discloses herein methods for treating Cushing's syndrome patients with a GRA (such as mifepristone) and ketoconazole. In embodiments, the patient suffers from Cushing's Disease.

Applicant discloses here methods for treating a Cushing's syndrome patient who is receiving ketoconazole treatment, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering said original dose of ketoconazole to said patient; and administering a glucocorticoid receptor antagonist (GRA) to the patient, wherein the amount of GRA administered is a first dose of GRA, whereby the patient is administered both ketoconazole and a GRA for treating Cushing's syndrome. In embodiments, the first dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole. In embodiments, the GRA is mifepristone.

In embodiments of such methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the first dose of GRA comprises an amount of GRA that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by said original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of a GRA and is not exposed to increased risk of ketoconazole toxicity. In embodiments, the first dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole. In embodiments, the GRA is mifepristone.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the administration of ketoconazole and of the GRA comprises concomitant administration of the original dose of ketoconazole and the first dose of said GRA.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the administration of the GRA comprises oral administration of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, ketoconazole and mifepristone are administered in a single liquid formulation comprising ketoconazole and mifepristone.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the first dose of the GRA is a dose of GRA selected from about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 900 mg, about 1000 mg, about 1200 mg, about 1500 mg, about 1800 mg, about 2000 mg, about 2100 mg, about 2400 mg, about 2700 mg, and about 3000 mg. In embodiments, the GRA is mifepristone, and the first dose of the GRA is a dose of mifepristone selected from about 1500 mg mifepristone, about 1200 mg mifepristone, about 900 mg mifepristone, about 600 mg mifepristone, and about 300 mg mifepristone.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods further comprise: administering a second dose of GRA, wherein said second dose is administered after the administration of the first dose of said GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of GRA comprises about the same amount of said GRA as the first dose of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of GRA comprises a lesser amount of said GRA than the first dose of GRA. In embodiments, the second dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of GRA comprises a greater amount of said GRA than the first dose of GRA. In embodiments, the GRA is mifepristone.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods further comprise: administering a subsequent dose of ketoconazole and a second dose of GRA, wherein the subsequent ketoconazole dose and the second GRA dose are both administered after the administration of the first dose of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of the GRA comprises about the same amount of the GRA as the first dose of the GRA, and the subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments, the second dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the subsequent dose of ketoconazole comprises a lesser amount of ketoconazole than the amount of the original dose of ketoconazole. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of the GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the second dose of the GRA comprises a greater amount of the GRA than the amount of said first dose of the GRA, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation comprising ketoconazole and the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the GRA is mifepristone, and the ketoconazole and the mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods further comprise: administration of a third dose of the GRA, wherein the third dose of the GRA is administered after the administration of the second dose of the GRA. In embodiments, the third dose of GRA is a lesser amount of GRA than would be administered in the absence of ketoconazole. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of GRA comprises about the same amount of the GRA as the second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA comprises a greater amount of the GRA than the second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA is administered after the administration of the second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA comprises about the same amount of GRA as the amount of said second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA comprises a lesser amount of the GRA than the amount of said second dose of the GRA. In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the third dose of the GRA comprises a greater amount of the GRA than the amount of said second dose of the GRA. In embodiments, the GRA is mifepristone.

In such embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant administration of ketoconazole and of the third dose of the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient simultaneously. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the ketoconazole and the GRA are administered to the patient in a single pill containing both ketoconazole and the GRA, or in a single liquid formulation comprising ketoconazole and the GRA. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the GRA is mifepristone, and the ketoconazole and the mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone.

In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with mifepristone and ketoconazole. In embodiments of methods of treating a Cushing's syndrome patient who is receiving ketoconazole treatment, the methods comprise concomitant treatment of the patient with mifepristone and ketoconazole, wherein the dose of ketoconazole administered concomitantly with ketoconazole is not reduced with respect to the ketoconazole dose administered to the patient in the absence of concomitant treatment with ketoconazole and mifepristone.

Applicant discloses herein a method for treating a Cushing's syndrome patient who is receiving ketoconazole treatment, said ketoconazole treatment comprising administering an original dose of ketoconazole to said patient, said method comprising: administering said original dose of ketoconazole to said patient; and administering mifepristone to the patient, wherein the amount of mifepristone administered is a first dose of mifepristone, whereby the patient is admin-

istered both ketoconazole and mifepristone for treating Cushing's syndrome. In embodiments, the first dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole.

In embodiments of methods for treating a Cushing's syndrome patient who is receiving ketoconazole treatment, wherein the ketoconazole treatment comprises administering an original dose of ketoconazole to said patient, the methods comprise administering a first dose of mifepristone that comprises an amount of mifepristone that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by said original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of mifepristone and is not exposed to increased risk of ketoconazole toxicity. In embodiments of such methods, the administration of ketoconazole and of mifepristone comprises concomitant administration of the original dose of ketoconazole and of the first dose of mifepristone. In embodiments of such methods, the administration of mifepristone comprises oral administration of mifepristone. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone. In embodiments of such methods, the first dose of mifepristone is a dose of about 300 milligrams (mg), about 600 mg, about 900 mg, about 1200 mg, or about 1500 mg.

In embodiments, such methods further comprise: administering a second dose of mifepristone, wherein said second dose is administered after the administration of the first dose of mifepristone. In embodiments, the second dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises about the same amount of mifepristone as the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the first dose of mifepristone. In embodiments, such methods further comprise administering a subsequent dose of ketoconazole and a second dose of mifepristone, wherein said subsequent dose and said second dose are both administered after the administration of the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises about the same amount of mifepristone as the first dose of mifepristone, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments of such methods, the subsequent dose of ketoconazole comprises a lesser amount of ketoconazole than the amount of the original dose of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the amount of said first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the amount of said first dose of mifepristone, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the original dose of ketoconazole. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone.

In embodiments, such methods further comprise administration of a third dose of mifepristone, wherein said third dose of mifepristone is administered after the administration of the second dose of mifepristone. In embodiments, the third dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the third dose of mifepristone comprises about the same amount of mifepristone as the second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a greater amount of mifepristone than the second dose of mifepristone. In embodiments, such methods further comprise administration of a third dose of mifepristone, wherein said third dose of mifepristone is administered after the administration of the second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises about the same amount of mifepristone as the amount of said second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a lesser amount of mifepristone than the amount of said second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a greater amount of mifepristone than the amount of said second dose of mifepristone. In embodiments, such methods comprise concomitant administration of ketoconazole and of the third dose of mifepristone. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient simultaneously. In embodiments of such methods, ketoconazole and mifepristone are administered to the patient in a single pill comprising both ketoconazole and mifepristone, or in a single liquid formulation comprising ketoconazole and mifepristone.

In embodiments of methods for treating a Cushing's syndrome patient who is receiving ketoconazole treatment at an original dose of ketoconazole, the methods comprise administering a first dose of mifepristone to the subject and reducing the dose of ketoconazole received by the patient to a ketoconazole dose that is less than the original ketoconazole dose, wherein the dose of mifepristone comprises an amount of mifepristone that is effective to aid in the treatment of Cushing's syndrome without substantially increasing the level of ketoconazole in the blood of the patient above that level produced by said original dose of ketoconazole, whereby the patient is administered both ketoconazole and an effective dose of mifepristone and is not exposed to increased risk of ketoconazole toxicity.

Accordingly, Applicant discloses herein a method for treating a Cushing's syndrome patient who is receiving ketoconazole at an initial dosage, said initial dosage comprising administering an initial dose of ketoconazole to said patient, said method comprising: administering a reduced dose of ketoconazole to said patient, wherein said reduced dose of ketoconazole is a dose of ketoconazole that is less than said initial dose by an amount of at least about 5% of the initial dose; and administering mifepristone to the patient, wherein the amount of mifepristone administered is a first dose of mifepristone, whereby the patient is administered both the reduced dose of ketoconazole and the first dose of mifepristone. In embodiments of such methods, the first dose of mifepristone comprises an amount of mifepristone that is effective to aid in the treatment of Cushing's syndrome, whereby the patient is administered both a reduced dose of ketoconazole and an effective dose of

mifepristone. In embodiments, the first dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the administration of ketoconazole and of mifepristone comprises concomitant administration of the reduced dose of ketoconazole and the first dose of mifepristone. In embodiments of such methods, the administration of mifepristone comprises oral administration of mifepristone. In embodiments of such methods, the first dose of ketoconazole is less than said initial dose of ketoconazole by an amount that is about 10%, about 15%, about 25%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 75%, or about 90% less than the initial dose. In embodiments of such methods, the first dose of mifepristone is a dose selected from about 300 mg, about 600 mg, about 900 mg, about 1200 mg, and about 1500 mg.

In embodiments, such methods further comprise administering a second dose of mifepristone, wherein said second dose is administered at a time after the administration of the first dose of mifepristone. In embodiments, the second dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises a lesser amount of mifepristone than the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises about the same amount of mifepristone as the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the first dose of mifepristone. In embodiments, such methods further comprise administering a subsequent dose of ketoconazole and a second dose of mifepristone, wherein said subsequent dose and said second dose are both administered at a time after the administration of both the reduced dose of ketoconazole and of the first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises about the same amount of mifepristone as the first dose of mifepristone, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the reduced dose of ketoconazole. In embodiments of such methods, the subsequent dose of ketoconazole comprises a lesser amount of ketoconazole than the amount of said reduced dose of ketoconazole. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the amount of said first dose of mifepristone. In embodiments of such methods, the second dose of mifepristone comprises a greater amount of mifepristone than the amount of said first dose of mifepristone, and said subsequent dose of ketoconazole comprises about the same amount of ketoconazole as the reduced dose of ketoconazole.

In embodiments, such methods further comprise administration of a third dose of mifepristone, wherein said third dose of mifepristone is administered at a time after the administration of the second dose of mifepristone. In embodiments, the third dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the third dose of mifepristone comprises a lesser amount of mifepristone than the second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises about the same amount of mifepristone as the second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a greater amount of mifepristone than the second dose of mifepristone.

In embodiments, such methods further comprise administration of a third dose of mifepristone, wherein said third dose of mifepristone is administered at a time after the administration of the second dose of mifepristone. In embodiments, the third dose of mifepristone is a lesser amount of mifepristone than would be administered in the absence of ketoconazole. In embodiments of such methods, the third dose of mifepristone comprises about the same amount of mifepristone as the amount of said second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a lesser amount of mifepristone than the amount of said second dose of mifepristone. In embodiments of such methods, the third dose of mifepristone comprises a greater amount of mifepristone than the amount of said second dose of mifepristone. In embodiments, such methods comprise administration of a dose of ketoconazole administered at the time as the administration of the third dose of mifepristone.

Applicant further discloses herein methods for treating a patient who is suffering from Cushing's syndrome with mifepristone, the patient also receiving concomitant administration of ketoconazole, said method comprising: to the patient concomitantly receiving ketoconazole, orally administering a dose of mifepristone that is a smaller dose of mifepristone than the dose that is an effective mifepristone dose when the patient receives only mifepristone. An effective dose of mifepristone when the patient receives only mifepristone for treating Cushing's syndrome is termed a "lone dose" of mifepristone. For example, the dose of mifepristone that is effective for the treatment of a Cushing's syndrome patient not concomitantly receiving ketoconazole or other treatment for Cushing's syndrome is a "lone dose" of mifepristone. In embodiments of the methods disclosed herein, for Cushing's syndrome patient receiving concomitant administration of ketoconazole, the dose of mifepristone is reduced by at least about 5% as compared to the lone dose of mifepristone. Accordingly, Applicant discloses herein a method for treating a Cushing's syndrome patient who is receiving ketoconazole, said method comprising: administering a reduced dose of mifepristone to said patient, wherein said reduced dose of mifepristone is a dose of mifepristone that is less than the lone dose of mifepristone as defined herein; whereby the patient is administered both ketoconazole and the reduced dose of mifepristone. In embodiments, such a reduced dose of mifepristone is an amount of mifepristone that is less than the lone dose of mifepristone by an amount that is at least about 5% of the lone dose. In embodiments of such methods, the reduced dose of mifepristone comprises an amount of mifepristone that is effective to aid in the treatment of Cushing's syndrome, whereby the patient is administered both a reduced dose of mifepristone and a dose of ketoconazole. In embodiments of such methods, the administration of ketoconazole and of mifepristone comprises concomitant administration of the reduced dose of mifepristone and the dose of ketoconazole. In embodiments of such methods, the administration of mifepristone comprises oral administration of mifepristone. In embodiments of such methods, the reduced dose of mifepristone is less than said lone dose of mifepristone by an amount that is about 10%, about 15%, about 25%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 60%, about 75%, or about 90% less than the lone dose. In embodiments of such methods, the reduced dose of mifepristone is a daily dose selected from about 900 mg, about 600 mg, about 300 mg, or is a dose of mifepristone selected from about 300 mg mifepristone administered every other day, a dose of about 300 mg mifepristone administered

every third day, and a dose of mifepristone of about 300 mg administered every fourth day.

Compositions

Applicant discloses herein compositions comprising a glucocorticoid receptor antagonist (GRA) which may be used in the treatment of a patient suffering from excess cortisol, e.g., in a patient suffering from Cushing's syndrome. In embodiments, the compositions comprising a GRA may be provided in an amount effective to control hyperglycemia secondary to hypercortisolism, and may be provided in an amount effective control hyperglycemia secondary to hypercortisolism in a patient suffering from endogenous Cushing's disease. In embodiments, the compositions comprising a GRA may be provided in an amount effective to control hyperglycemia secondary to hypercortisolism in a patient suffering from endogenous Cushing's disease, where the patient has failed surgery, or is not a candidate for surgery.

Applicant also discloses herein compositions comprising a glucocorticoid receptor antagonist (GRA) and ketoconazole. These compositions comprising a GRA and ketoconazole may be used in the treatment of a Cushing's syndrome patient.

The compositions as disclosed herein can be prepared in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. The compositions of the present invention can also be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compositions disclosed herein can be administered by inhalation, for example, intranasally. Additionally, the compositions of the present invention can be administered transdermally. The compositions disclosed herein can also be administered by intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, J. Clin. Pharmacol. 35:1187-1193, 1995; Tjwa, Ann. Allergy Asthma Immunol. 75:107-111, 1995).

Accordingly, in embodiments disclosed herein, the compositions include pharmaceutical compositions including a pharmaceutically acceptable carrier or excipient, a glucocorticoid receptor antagonist (GRA), and a SI. SIs include, for example, ketoconazole, levoketoconazole, metyrapone, aminoglutethimide, etomidate, LCI699 (Osilodrostat), and others.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Mack Publishing Co, Easton Pa. ("Remington's").

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5% or 10% to 70% of ketoconazole and/or the GRA.

Suitable solid excipients include, but are not limited to, magnesium carbonate; magnesium stearate; talc; pectin; dextrin; starch; tragacanth; a low melting wax; cocoa butter; carbohydrates; sugars including, but not limited to, lactose, sucrose, mannitol, or sorbitol, starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins including, but not limited to, gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound (i.e., dosage). Pharmaceutical preparations of the invention can also be used orally using, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain ketoconazole and/or the GRA mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, ketoconazole and/or the GRA may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and ketoconazole and/or the GRA are dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving ketoconazole and/or the GRA in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

Oil suspensions can be formulated by suspending ketoconazole and/or the GRA in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, J. Pharmacol. Exp. Ther. 281:93-102, 1997. The pharmaceutical formulations of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be formulated for administration via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, J. Biomater Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao Pharm. Res. 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. Pharm. Pharmacol. 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months.

In another embodiment, the compositions of the present invention can be formulated for parenteral administration, such as intravenous (IV) administration or administration into a body cavity or lumen of an organ. The formulations for administration will commonly comprise a solution of the compositions of the present invention dissolved in a pharmaceutically acceptable carrier. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. These formulations may be sterilized by conventional, well known sterilization techniques. The formulations may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of the compositions of the present invention in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. For IV administration, the formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol.

In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, e.g., Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, Curr. Opin. Biotechnol. 6:698-708, 1995; Ostro, Am. J. Hosp. Pharm. 46:1576-1587, 1989).

Administration

The compositions disclosed herein can be delivered by any suitable means, including oral, parenteral and topical methods. Transdermal administration methods, by a topical route, can be formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the GRA and ketoconazole. In embodiments, the GRA is mifepristone. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The GRA and ketoconazole can be co-administered or administered separately. Concomitant administration includes administering ketoconazole within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of the GRA. Concomitant administration also includes administering the GRA and ketoconazole simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. Moreover, the GRA and ketoconazole can each be administered once a day, or two, three, or more times per day so as to provide the preferred dosage level per day. In embodiments, the GRA is mifepristone.

In some embodiments, concomitant administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both the GRA and ketoconazole. Suitable co-formulations include single pharmaceutical compositions including a GRA, ketoconazole, and a pharmaceutically acceptable excipient. In embodiment, the GRA is mifepristone.

In other embodiments, the GRA and ketoconazole can be formulated separately.

Ketoconazole can be present in any suitable amount, and can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. Suitable dosage ranges for ketoconazole in combination

with the GRA, include from about 0.1 mg to about 10,000 mg, or about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg. Suitable dosages for ketoconazole in combination with the GRA, include about 1 mg, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or 1000 mg. In embodiments, the GRA is mifepristone.

Similarly, the GRA can be present in combination with ketoconazole in any suitable amount. The amount of GRA can depend on various factors including, but not limited to, weight and age of the subject, state of the disease, etc. Suitable dosage ranges for the GRA in combination with the SI, include from about 0.1 mg to about 10,000 mg, or about 1 mg to about 1000 mg, or about 10 mg to about 750 mg, or about 25 mg to about 500 mg, or about 50 mg to about 250 mg. Suitable dosages for the GRA in combination with ketoconazole, include, but are not limited to, about 1 mg, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900 or about 1000 mg. In embodiments, the GRA is mifepristone,

Ketoconazole and the GRA can be present in the compositions of the present invention in any suitable weight ratio, such as from about 1:100 to about 100:1 (w/w), or about 1:50 to about 50:1, or about 1:25 to about 25:1, or about 1:10 to about 10:1, or about 1:5 to about 5:1 (w/w). Ketoconazole and the GRA can be present in any suitable weight ratio, such as about 1:100 (w/w), 1:50, 1:25, 1:10, 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, 5:1, 10:1, 25:1, 50:1 or 100:1 (w/w). Other dosages and dosage ratios of ketoconazole and the GRA are suitable in the compositions and methods disclosed herein. In embodiments, the GRA is mifepristone.

The composition can also contain other compatible therapeutic agents. The compounds described herein can be used in combination with one another, or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

Kits

Applicant further provides kits including compositions as disclosed herein. Kits may also include instructions for the use of the compositions.

In embodiments, a kit includes: a pharmaceutical composition containing ketoconazole; and a pharmaceutical composition containing a GRA. In embodiments, the GRA is mifepristone.

In embodiments, a kit includes: a pharmaceutical composition containing ketoconazole; and a pharmaceutical composition containing a GRA; and instructions for the use (e.g., administration) of the ketoconazole and the GRA. In embodiments, the GRA is mifepristone, and the instructions include instructions for the administration of mifepristone. In embodiments, the instructions include instructions regarding one or more of the number of pharmaceutical compositions to be taken each day, the timing of such administration, whether or not the pharmaceuticals are to be taken with food or in a fasted state, contraindications, possible side effects, activities to be avoided during treatment with the pharmaceutical compositions (if any), and foods to be avoided during treatment with the pharmaceutical compositions (if any).

In embodiments, a kit includes: a pharmaceutical composition containing ketoconazole and a GRA. In embodiments, the GRA is mifepristone, and the pharmaceutical composition contains ketoconazole and mifepristone.

In embodiments, a kit includes: a pharmaceutical composition containing ketoconazole and a GRA; and instructions for the use (e.g., administration) of the pharmaceutical composition. In embodiments, the GRA is mifepristone. In embodiments of the kits disclosed herein, the pharmaceutical composition includes ketoconazole and mifepristone, and the instructions include instructions for the administration of the pharmaceutical containing ketoconazole and mifepristone. In embodiments, the instructions include instructions regarding one or more of the number of pharmaceutical compositions to be taken each day, the timing of such administration, whether or not the pharmaceutical composition is to be taken with food or in a fasted state, contraindications, possible side effects, activities to be avoided during treatment with the pharmaceutical composition (if any), and foods to be avoided during treatment with the pharmaceutical composition (if any).

## EXAMPLES

The following examples are presented by way of illustration of embodiments of the methods disclosed herein, and serve to illustrate, but not to limit, the present disclosure of methods of treating patients suffering from Cushing's syndrome, including Cushing's Disease; or from prostate cancer and other androgen-sensitive cancers; or from breast cancer, ovarian cancer, or other cancer hormone-sensitive cancer (e.g., cancer sensitive to estrogen or progesterone); and patients suffering from other diseases, disorders, or syndromes.

### Example 1

A study was performed in order to determine the effect of oral ketoconazole at a dose of 400 mg once per day (OD) or 200 mg twice per day (BID) on the plasma pharmacokinetics of a 300 mg single dose of mifepristone given to a fasted subject, in comparison to previous study data. This study was an open-label study in healthy male subjects.

Healthy male volunteers between the ages of 18 to 45 years of age with a body mass index (BMI) ranging between 19 and 32 kg/m2 and a weight of at least 60 kg (132 lbs) were enrolled. Subjects had no clinically significant abnormal findings on the physical examination, ECG, blood pressure, heart rate, medical history, or clinical laboratory results during screening. The QTc interval at screening was less than 450 msec.

In cohort 1, six subjects received ketoconazole 400 mg OD for 14 days. The cohort 1 subjects participated in a screening visit to assess eligibility, and in a check-in day during which eligibility was re-confirmed and the first dose of 400 mg oral ketoconazole given at approximately 8 PM (12 hours prior to expected time of Day 1 mifepristone dose).

The morning of Day 1, subjects received 400 mg oral ketoconazole fasted, 0.5 hour prior to receiving the 300 mg single dose of mifepristone fasted. Subjects remained in the clinic on Days 2 and 3 to receive 400 mg OD oral ketoconazole fasted, and for safety evaluation and collection of blood pharmacokinetic (PK) samples. Subjects were discharged from the clinic on Day 4 following administration of 400 mg OD oral ketoconazole fasted, and returned to the clinic the mornings of Days 5 through 13 to receive 400 mg OD oral ketoconazole fasted.

In cohort 2, six subjects received ketoconazole 200 mg BID for 14 days. The 300 mg single dose of mifepristone was given to all subjects on day 1. All 12 subjects completed the study. Cohort 2 subjects participated in a Screening visit to assess eligibility and a check-in Day (Day −1) during which eligibility was re-confirmed. On Day 0, subjects

received 200 mg BID oral ketoconazole: the morning dose after an overnight fast and the evening dose 12 hours prior to expected time of Day 1 Mifepristone dose. The morning of Day 1, subjects received 200 mg oral ketoconazole fasted, 0.5 hour prior to receiving the 300 mg single dose of Mifepristone fasted. The evening of Day 1, subjects received 200 mg oral ketoconazole. Subjects remained in the clinic on Days 2, 3 and 4 to receive 200 mg BID oral ketoconazole, and for safety evaluation and collection of blood pharmacokinetic (PK) samples. Subjects were discharged from the clinic on Day 4 following evening administration of 200 mg oral ketoconazole, and returned to the clinic the morning and evening of Days 5 through 13 to receive 200 mg BID oral ketoconazole. Morning doses of ketoconazole on Days 0-13 were administered in the fasted state.

Subjects in both cohorts had blood sampling for determination of plasma concentrations of mifepristone and its metabolites within 30 minutes before mifepristone dosing and at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72 (Day 4), 120 (Day 6), 192 (Day 9), 264 (Day 12), and 336 (Day 15) post mifepristone dose. Subjects in both cohorts returned to the study center on Day 15 for safety monitoring, and completion of the Termination Visit procedures, followed by discharge from the study. Safety was assessed by spontaneously reported adverse events, physical examinations, and routine clinical laboratory tests. To the extent possible, any adverse events deemed study drug-related and that were ongoing at the time of discharge from the study were followed-up to resolution or until a determination is made that the unresolved event was stable.

No subject experienced a serious adverse effect (SAE), or an adverse event (AE) that resulted in discontinuation from the study. Three subjects (25%) experienced at least 1 treatment-emergent adverse event (TEAE). All TEAEs were mild in intensity. No TEAE was considered by the investigator to be related to mifepristone. One TEAE of insomnia was considered by the investigator to be related to ketoconazole.

Minimal changes in laboratory test results were observed during the course of the study. No laboratory test result was considered by the investigator to be a TEAE. Any abnormal values or shifts from baseline were considered not clinically significant. No clinically significant changes in any electrocardiogram (ECG) parameter were observed.

Pharmacokinetics (PK): Blood samples were drawn within 30 minutes before mifepristone dosing and at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72 (Day 4), 120 (Day 6), 192 (Day 9), 264 (Day 12), and 336 (Day 15) post mifepristone dose. Pharmacokinetic parameters were calculated for plasma concentrations of mifepristone and its metabolites following the single dose at Day 1. Descriptive statistics (count, mean, median, standard deviation, minimum, maximum, and % coefficient of variation) were provided. Mifepristone/metabolite concentrations were listed and summarized. Comparisons with previous study data were made. The mean PK parameters from this study are presented in Table 1 ("MIFE" indicates mifepristone). The abbreviations and symbols used in Table 1 have the following meanings: "Tmax" indicates time to maximum observed plasma concentration; "Tmin" indicates time to minimum observed concentration within the 24 hour dosing interval; "Cmax" indicates maximum observed plasma concentration; "Cmin" indicates minimum observed concentration within the 24 hour dosing interval; "Cavg" indicates average steady-state concentration and is defined as drug input rate (Ro) divided by drug removal rate (CLss) (Cavg=Ro/CLss, where f (the fraction absorbed) cancels out (f is a factor of both Ro and CLss); this equation reduces to Cavg=AUCtau/tau); "AUC0-24" indicates area under the plasma concentration versus time curve from time 0 to 24 hours post-dose, calculated using the linear trapezoidal rule (this is the same as AUCtau where tau is 24 hours or 1 day); "% Fluct" indicates percent fluctuation in drug concentrations at steady-state computed as % Fluct=100×(Cmax−Cmin)/Cavg.

PHARMACOKINETIC (PK) RESULTS: Mifepristone plasma concentrations showed a rapid initial decline followed by a slow decline over time. At later time points, concentrations showed an accelerated decline indicative of non-linear kinetics. Metabolites peaked later relative to parent mifepristone as would be expected. Mifepristone metabolite RU 42633 exposure was similar or even greater than that for mifepristone, while RU 42698 (a mifepristone metabolite) exposure was approximately 0.74 to 0.94 relative to mifepristone and RU 42848 (also a mifepristone metabolite) exposure was 0.53 to 0.68 relative to mifepristone. With increase in time interval, the fraction of AUC relative to mifepristone accounted for by metabolite increased.

Cohort 2 Cmax (where Cmax is the maximum observed plasma concentration) and AUCinf (where AUCinf is the area under the concentration-time curve from time of last dose to infinity) were similar to corresponding parameters in Cohort 1. The geometric mean ratio (GMR) for Cmax was 1.15 and that for AUCinf was 1.05. However, the 90% confidence intervals around the GMR were higher than the standard 80:125 reference interval. Thus, there may be a small increase in mifepristone exposure with a divided ketoconazole dose (200 mg BID vs. 400 mg OD), but this was minor. Terminal half-life was approximately the same in Cohort 2 versus Cohort 1 and Tmax was shorter for Cohort 2 versus Cohort 1.

SAFETY RESULTS: Among 12 subjects who received mifepristone, 3 (25%) experienced at least one treatment emergent adverse event (TEAE). All TEAEs were mild in intensity. No TEAE was considered by the investigator to be related to Mifepristone. One TEAE of insomnia was considered by the investigator to be related to ketoconazole. No subject experienced an SAE or an AE that resulted in discontinuation from the study. Minimal changes in laboratory test results were observed for subjects during the course of the study. No laboratory test result was considered by the investigator to be a TEAE. Any abnormal values or shifts from Baseline values were considered not clinically significant. No clinically significant changes in any ECG parameter were observed.

While PK parameters in Cohort 2 were similar to those in Cohort 1, the 90% confidence intervals around the GMR were higher than the standard 80:125 reference interval used for bioequivalence testing. Thus, there may be a small and minor increase in mifepristone exposure with a divided ketoconazole dose (200 mg BID vs. 400 mg OD). Terminal half-life was approximately the same in Cohort 2 versus Cohort 1 and Tmax was shorter for Cohort 2 versus Cohort 1. Mifepristone 300 mg was safe and well tolerated in healthy volunteers under the following treatment regimens: single-dose fasted with ketoconazole 400 mg OD for 14 days or ketoconazole 200 mg BID for 14 days.

## Example 2

The primary objective of this study was to determine the effect of a 400 mg single dose of ketoconazole on the PK of an 8-day regimen of 300 mg or 600 mg OD mifepristone

given following a moderate fat (34%) breakfast. This was an open-label study in healthy male subjects. In cohort 1, six subjects received mifepristone 300 mg OD for 8 days. In cohort 2, six subjects received mifepristone 600 mg OD for 8 days. The 400 mg single dose of ketoconazole was given to all subjects on day 8. Three subjects discontinued early from the study: one subject in cohort 1 due to new onset sinus bradycardia, and two subjects in cohort 2 due to withdrawn consent.

METHODOLOGY: Twelve subjects were enrolled, six in Cohort 1 and 6 in Cohort 2. Three subjects discontinued early from the study, one subject in Cohort 1 due to an adverse event of sinus bradycardia, and two subjects in Cohort 2 due to withdrawn consent.

Cohort 1: Subjects participated in a Screening visit to assess eligibility, and returned to the clinic on Days 1-6 to receive 300 mg oral mifepristone following a moderate fat breakfast. On Day 7 subjects were admitted to the clinic in the fasted state for a pre-dose PK blood draw, after which they received 300 mg oral mifepristone following a moderate fat breakfast. Subjects had serial blood sampling for determination of mifepristone and its metabolites at hours 0.5, 1, 2, 4, 6, 8, and 12 post Day 7 dose. On Day 8, a pre-dose PK sample was drawn within 30 minutes prior to ketoconazole dosing for determination of plasma concentrations of mifepristone and its metabolites and ketoconazole. Following a moderate fat breakfast on Day 8, subjects received 400 mg ketoconazole 0.5 hours prior to 300 mg mifepristone and had serial blood sampling at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 120 post mifepristone dose for determination of plasma concentrations of mifepristone and its metabolites; and at hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 post ketoconazole dose for determination of plasma concentrations of ketoconazole. Subjects were discharged on Day 11.

Cohort 2: Subjects participated in a Screening visit to assess eligibility and returned to the clinic on Days 1-6 to receive 600 mg oral mifepristone following a moderate fat breakfast. On Day 7 subjects were admitted to the clinic in the fasted state for a pre-dose PK blood draw, after which they received 600 mg oral mifepristone following a moderate fat breakfast. Subjects had serial blood sampling for determination of mifepristone and its metabolites at hours 0.5, 1, 2, 4, 6, 8, and 12 post Day 7 dose. On Day 8, a pre-dose PK sample was drawn within 30 minutes prior to ketoconazole dosing for determination of plasma concentrations of mifepristone and its metabolites and ketoconazole. Following a moderate fat breakfast on Day 8, subjects received 400 mg ketoconazole 0.5 hours prior to 600 mg mifepristone and had serial blood sampling at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 120 post mifepristone dose for determination of plasma concentrations of mifepristone and its metabolites; and at hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 post ketoconazole dose for determination of plasma concentrations of ketoconazole. Subjects were discharged on Day 11. Subjects in both cohorts returned to study center on Day 13 for safety monitoring, collection of the 120-hour PK draw, and completion of the Termination Visit procedures, followed by discharge from the study. To the extent possible, any adverse events deemed study drug-related and that were ongoing at the time of discharge from the study were followed-up to resolution or until a determination was made that the unresolved event was stable.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Healthy male volunteers between the ages of 18 to 45 years of age with a body mass index (BMI) ranging between 19 and 32 kg/m2 and a weight of at least 60 kg (132 lbs) were enrolled. Subjects had no clinically significant abnormal findings on the physical examination, ECG, blood pressure, heart rate, medical history, or clinical laboratory results during screening. The QTc interval at screening was less than 450 msec.

DURATION OF TREATMENT: Up to a total of 28 days, including up to 2 weeks screening, dosing on Days 1-8, safety observation, and PK sample collection through Day 13. For measuring the pharmacokinetics of mifepristone, samples were collected within 30 minutes before Day 7 mifepristone dose and at hours 0.5, 1, 2, 4, 6, 8, and 12 post Day 7 mifepristone dose; within 30 minutes before Day 8 ketoconazole dosing and at hours 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 120 post Day 8 mifepristone dose. For measuring the pharmacokinetics of ketoconazole, samples were collected predose on Day 8 (24 hr sample from Day 7), and at hours 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post ketoconazole dose.

Safety was assessed by spontaneously reported adverse events, physical examinations, and routine clinical laboratory tests. Adverse event data were tabulated. Physical findings and laboratory test results were listed by subject.

SAFETY RESULTS: No subject experienced an SAE. Among twelve subjects who received mifepristone, six subjects (50%) experienced at least 1 TEAE. TEAEs were predominantly mild in intensity. The majority of subjects (5/6) with TEAEs were in Cohort 2 and onset of the majority of TEAEs occurred on or after Day 8 during treatment with both ketoconazole and mifepristone 600 mg. TEAEs considered possibly or probably related to mifepristone administration in four subjects in Cohort 2 were dizziness, nausea, vomiting, dry mouth, and rash. One TEAE of headache was considered by the investigator to be possibly related to both ketoconazole and mifepristone administration. One subject in Cohort 1 with a TEAE of nodal arrhythmia on Day 8 was withdrawn by the investigator. The event was considered mild in severity and not considered related to study medication. The corresponding ECG abnormality noted as "sinus bradycardia" was considered not clinically significant. No subject experienced an SAE.

Minimal changes in laboratory test results were observed for subjects during the course of the study. No laboratory test result was considered by the investigator to be a TEAE. There were no clinically significant changes or abnormalities in vital signs, physical examinations or body weights during the study. Abnormal ECGs occurred in four subjects and no abnormality was considered clinically significant.

STATISTICAL METHODS: Pharmacokinetics (PK): Pharmacokinetic parameters Cmax, Ctrough, and interdosing interval AUC were calculated for plasma concentrations of mifepristone and its metabolites following dose on Days 7 and 8. Descriptive statistics (count, mean, median, standard deviation, minimum, maximum, and % coefficient of variation) were provided. mifepristone/metabolite concentrations were listed and summarized. GM means of Cmax and AUC0-24 were compared for Day 8 to Day 7 in this study and also to combined data of 300 mg OD mifepristone in previous multiple dose studies. Additionally, comparisons were made between the PK results of cohort 1 and 2. Pharmacokinetic parameters Cmax, T1/2 and total AUC were calculated for plasma concentrations of ketoconazole following the single dose on Day 8. Descriptive statistics (count, mean, median, standard deviation, minimum, maximum, and % coefficient of variation) were provided. Ketoconazole concentrations were listed and summarized. GM means of Cmax and total AUC were compared for the single

dose in this study to the combined data of reported 400 mg single doses of ketoconazole of healthy subjects from the literature.

The mean (±SD) age of subjects was 29.4±6.8 years, and the mean BMI at screening was 25.61±3.27 kg/m2. Seven of twelve subjects (58.3%) were White, and 5/12 (41.7%) were Black/African American. Five of the 12 subjects (41.7%) were of Hispanic or Latino ethnicity.

PHARMACOKINETIC (PK) RESULTS: PK data for mifepristone and metabolites was available for eleven of the 12 enrolled subjects and data for ketoconazole PK analyses was available for 10 subjects. Concentrations of mifepristone and each metabolite were above the limits of detection during the entire sampling duration from Day 7 predose to Day 13 (end of study). mifepristone plasma concentrations showed a rapid initial decline followed by a slow decline over time and metabolites peaked later relative to parent mifepristone as expected. Mean RU 42633 and RU 42848 exposure was similar or even greater than that for mifepristone, while RU 42698 exposure was lower. Ketoconazole PK after a single dose on Day 8 was readily computed. Co-administration of ketoconazole increased mifepristone and metabolite exposure. In the presence of 400 mg ketoconazole on Day 8, Cohort 1 mifepristone Cmax and AUC0-24 increased by 20% and 25% relative to the prior Day 7 without ketoconazole. This effect was slightly greater at 600 mg OD mifepristone in Cohort 2, where Cmax and AUC0-24 increased by 39% and 28% between Day 7 and Day 8. A dose of 600 mg OD mifepristone (Cohort 2) resulted in higher mifepristone and metabolite exposure relative to a dose of 300 mg OD (Cohort 1) both alone and in the presence of 400 mg ketoconazole. This increase was less than proportionate to the two-fold dose increment. On Day 7 without ketoconazole, mifepristone Cmax and AUC0-24 at 600 mg OD were 42% and 48% greater than at 300 mg OD. This dose effect was greater in the presence of 400 mg ketoconazole. Day 8 mifepristone Cmax and AUC0-24 were 65% and 52% greater at 600 mg OD than at 300 mg OD. mifepristone half-life on Day 8 in the presence of 400 mg ketoconazole was similar between the two mifepristone dose levels. Day 8 half-life was 13% greater at 600 mg OD than at 300 mg OD. Ketoconazole exposure following a single 400 mg dose on Day 8 of a regimen of 600 mg OD mifepristone was 37% and 36% higher (Cmax and AUCinf) relative to a mifepristone regimen of 300 mg OD. Ketoconazole half-life on either mifepristone regimen was not appreciably different. The addition of a single dose of 400 mg ketoconazole to 300 mg or 600 mg OD mifepristone on Day 8 resulted in exposure increases in Cmax and AUC0-24 that were similar to historical values at 600 mg or 1200 mg OD in the fasted state and 1200 mg OD in the fed state, respectively. Although the increase in exposure due to the addition of ketoconazole was only between 20% and 39% in absolute terms, the resulting exposure was similar to that of a dose 2 to 3 times greater. This is believed to be due to a lack of dose-proportional kinetics for mifepristone.

The mean PK parameters and results from this study are presented in Table 2.

The abbreviations and symbols used in Table 2 have the following meanings:

"Tmax" indicates time to maximum observed plasma concentration; "Tmin" indicates time to minimum observed concentration within the 24 hour dosing interval; "Cmax" indicates maximum observed plasma concentration; "Cmin" indicates minimum observed concentration within the 24 hour dosing interval; "Cavg" indicates average steady-state concentration and is defined as drug input rate (Ro) divided by drug removal rate (CLss) (Cavg=Ro/CLss, where f cancels out; this equation reduces to Cavg=AUCtau/tau); "AUC0-24" indicates area under the plasma concentration versus time curve from time 0 to 24 hours post-dose, calculated using the linear trapezoidal rule (this is the same as AUCtau where tau is 24 hours or 1 day); "% Fluct" indicates percent fluctuation in drug concentrations at steady-state computed as % Fluct=100×(Cmax−Cmin)/Cavg.

Drug-drug interaction (DDI) effects of ketoconazole on mifepristone and of mifepristone on ketoconazole were studied. A single 400 mg dose of ketoconazole caused a detectable increase in mifepristone exposure at mifepristone doses of 300 and 600 mg OD, and mifepristone at these doses caused a detectable increase in ketoconazole exposure. Although the increase in mifepristone exposure due to the addition of ketoconazole was only between 20% and 39% in absolute terms, the resulting exposure was similar to that of a dose 2 to 3 times greater. This is believed to be due to a lack of dose-proportional kinetics for mifepristone. Predominantly mild AEs occurred and were observed primarily in subjects administered ketoconazole and mifepristone 600 mg.

## Example 3

A Phase 1, single-center, open-label study was performed to study the effect of oral twice-daily doses of 200 mg of ketoconazole given with multiple oral once-daily doses of 600 mg of mifepristone in healthy male volunteers, during which all drug administrations were given after a typical meal (34% fat content). An objective of this study was to determine the effect of ketoconazole 200 mg twice daily on the PK of mifepristone 600 mg once daily when both drugs were administered with food. A single dose of ketoconazole was administered on Day-1. During multidose administration, mifepristone was administered on Days 1-17 and ketoconazole on Days 13-17; follow-up continued on Days 18-31. Sixteen subjects were enrolled (mean age 31.9 years; 8 black, 6 white, 2 other), and two subjects discontinued before starting the mifepristone/ketoconazole combination treatment.

The study was a two period study design. In Period 1: 600 mg mifepristone was administered once daily from Day 1 to Day 12; pharmacokinetic samples were taken before each dose for assay of mifepristone and active metabolites (mono-demethylated metabolite, RU 42633; hydroxylated metabolite, RU 42698; and di-demethylated metabolite, RU 42848) to confirm that steady-state was achieved, and for a dose-interval concentration-profile on Day 12. In Period 2: 600 mg mifepristone once daily was continued in combination with 200 mg ketoconazole twice daily from Days 13 to 17; pharmacokinetic samples were taken for assay of both mifepristone and metabolites, and ketoconazole before dosing on Days 13 to 17, and on Day 17 for a dose-interval concentration-time profile

A secondary objective was to determine if the effect of 200 mg BID ketoconazole on the PK of co-administered 600 mg OD mifepristone at steady-state exceeded exposure to mifepristone and metabolites compared to that of 1200 mg OD mifepristone with food, the labeled dosing regimen with the highest mean observed exposure in healthy subjects.

Effects of Co-Administration with Ketoconazole on Mifepristone and Metabolites: The concentrations of mifepristone and the hydroxylated metabolite, RU 42698, were higher on Day 17 (600 mg mifepristone daily co-administered with 200 mg ketoconazole twice daily) than on Day 12

(mifepristone alone). Concentrations of RU 42633 and RU 42848 were similar on Day 17 and Day 12. Results of the formal statistical analysis are shown in Table 3.

For mifepristone, the geometric mean ratio of test to reference for $C_{max}$ was 127.59% (90% CI: 116.66, 139.54, where "CI" means "confidence interval" and "90% CI" means "90% confidence interval") and for $AUC_{0-24}$ was 138.01% (90% CI: 127.12, 149.84). The lower bound of the 90% confidence intervals exceeded 100% and the upper bound exceeded 125%. Thus, co-administration with ketoconazole increased mifepristone exposure. Similarly, for metabolite RU 42698, the lower bounds of the 90% confidence intervals exceeded 100% and both geometric mean ratios and the upper bound of the 90% confidence interval exceeded 125%, and thus exposure to this metabolite was increased by ketoconazole.

For metabolites RU 42848 and RU 42633, the calculated geometric mean ratios and 90% confidence intervals of exposure ratios were within the standard 80:125 comparison interval and thus not affected by ketoconazole.

Effects of Co-administration with mifepristone on Ketoconazole: The plasma concentration-time profiles of ketoconazole given twice daily with mifepristone on Day 17 were much higher than for ketoconazole given as a single dose alone on Day-1. Results of the formal statistical analysis are shown in Table 4.

The geometric mean ratio of test to reference for $C_{max}$ was 252.71% (90% CI: 214.85, 297.26) and for AUC was 365.36% (90% CI: 333.78, 399.93). Thus, the geometric mean ratio and both lower and upper bounds of the 90% confidence intervals were entirely above the standard 80:125 comparison interval and exposure on Day 17 (with mifepristone) was higher than on Day-1 (ketoconazole alone).

Comparison of Mifepristone Exposure with mifepristone Labeled Doses: The concentration-time plots showed that mean mifepristone concentrations on Day 17 in the present study were less than those in the fed condition in a previous "historic" study in which subjects received 1200 mg mifepristone daily for seven days. Mifepristone was administered to the subjects within thirty minutes following a typical meal (34% fat) in both the present study and in the historic study. Results of the formal statistical analysis are shown in Table 5.

For mifepristone, the geometric mean ratio of test to reference for $C_{max}$ was 84.64% (90% CI: 72.92, 98.23); for $AUC_{0-24}$ it was 87.27% (90% CI: 74.72, 101.94). The 90% confidence intervals were below and overlapping the standard 80:125 comparison interval. The mean mifepristone concentrations in subject receiving 600 mg mifepristone following a 34% fat meal were less than the mifepristone concentrations in the historic study. As shown in Table 5, administration of 600 mg mifepristone in the fed state with ketoconazole resulted in mifepristone concentrations that were less than the mifepristone concentrations measured in subjects receiving 1200 mg mifepristone daily in the absence of ketoconazole. The Geometric Mean Ratio (GMR) values in Table 5 suggest that mifepristone 600 mg co-administered with ketoconazole yields mifepristone exposure 13-15% less than that of 1200 mg mifepristone in the absence of ketoconazole; for the metabolites, corresponding values range from an 18-19% decrease to a 17-18% increase. Thus, administration of 600 mg mifepristone daily with ketoconazole resulted in mifepristone concentrations that were not higher than the mean observed exposure at 1200 mg mifepristone; both treatments given following typical 34% fat meal. The value of 87% for GMR of the AUCs suggests that 900 mg mifepristone in the presence of ketoconazole would better match the exposure of a subject to 1200 mg mifepristone alone than would 600 mg mifepristone in the presence of ketoconazole. Thus, these data also support the use of 900 mg mifepristone, and higher doses as well, in the presence of ketoconazole.

For metabolite RU 42633, the 90% confidence intervals were within the standard interval for $C_{max}$ (geometric mean ratio 96.31%) and just overlapping the lower bound of the standard interval for $AUC_{0-24}$ (geometric mean ratio 91.34%). For metabolite RU 42698, confidence intervals for both $C_{max}$ and $AUC_{0-24}$ were overlapping and above the standard interval (geometric mean ratio $C_{max}$: 116.55%; $AUC_{0-24}$: 118.18%). For metabolite RU 42848, the 90% confidence intervals were overlapping and below the standard interval for $C_{max}$ (geometric mean ratio 82.45%) and $AUC_{0-24}$ (ratio 81.43%).

RU 42698 is a relatively minor metabolite and comprises 9% of the total steady-steady $AUC_{0-24}$ of mifepristone, RU42633, RU42698, RU42848 alone and 13% of the total steady-steady $AUC_{0-24}$ in the presence of ketoconazole. Therefore, the increase in RU 42698 $AUC_{0-24}$ in the presence of ketoconazole is considered to be minor.

FIG. **1** illustrates the results of measurements of plasma levels of mifepristone, RU42633, RU42698, and RU 42848. These measurements were made prior to the daily administration of mifepristone to the subject; thus the mifepristone and metabolite concentrations are "trough" concentrations. These results show that trough concentrations of mifepristone and RU42848 were increasing day-by-day through the start of ketoconazole administration (Day 13). This indicates that steady state conditions may not have been attained at the time of ketoconazole administration (which began on day 13).

FIG. **2** shows the plasma concentration profile of mifepristone before and after inhibition of CYP3A by ketoconazole. Applicant notes that the time 0 values (pre-dose) differ by ~500 ng/ml, a difference that is maintained relatively constant throughout much of the 24-hour sampling interval. Thus, if the daily increase in trough concentrations between days 7 and 12 persevered through day 17, an unknown fraction of the increased AUC (and Cmax) between Day 12 and Day 17 could be due to further mifepristone administration rather than by an effect of ketoconazole alone. Thus, the values reported in Table 3 may overstate the impact of CYP3A inhibition on exposure to mifepristone (and RU42848).

CONCLUSIONS: Co-administration of 600 mg mifepristone once daily with 200 mg ketoconazole twice daily resulted in a mean increase in exposure to mifepristone of approximately 28% ($C_{max}$: geometric mean ratio 127.59% [90% CI: 116.66, 139.54]) and 38% ($AUC_{0-24}$: geometric mean ratio 138.01% [90% CI: 127.12, 149.84]). These exposures are approximately 85% of those observed following the highest labeled dose of mifepristone (1200 mg daily).

The mean increase in exposure to the hydroxylated metabolite, RU 42698 (approximately 70%), was somewhat greater than the increase in exposure to parent, resulting in exposure that was approximately 15 to 20% higher than that following the highest labeled dose of mifepristone. In contrast, co-administration with ketoconazole resulted in little change in exposure to the mono-demethylated metabolite, RU 42633, or di-demethylated metabolite, RU 42848; exposure to these metabolites was similar to or slightly lower than exposure following the highest labeled dose.

The results presented in this example indicate that, with inhibition of CYP3A (e.g., by co-administration of a strong CYP3A inhibitor such as ketoconazole), a subject adminis-

tered 900 mg mifepristone daily would experience corresponding increases in mifepristone Cmax and AUC of 27.59% and of 38.01%, respectively, which should yield systemic exposures similar in magnitude to those previously attained with 1200 mg daily. Thus, the results of these measurements indicate that a subject, previously receiving a dose of 1200 mg mifepristone daily, may be safely administered a dose of 900 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen. Similarly, the results of these measurements indicate that a subject, previously receiving a dose of 900 mg mifepristone daily, may be safely administered a dose of 600 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen. In addition, the results of these measurements indicate that a subject, previously receiving a dose of 600 mg mifepristone daily, may be safely administered a dose of 300 mg mifepristone daily when a strong CYP3A inhibitor such as ketoconazole is added to the regimen.

No deaths or SAEs were reported during the study. Two subjects discontinued due to AEs (moderate hypertension in one subject and moderate bilateral rash on the upper arms and thighs in the other subject, both during the mifepristone-only treatment period). At least one TEAE was reported in 55.6% (9 of 16) of the subjects during treatment with mifepristone alone, in 57.1% (8 of 14) of the subjects during the mifepristone/ketoconazole treatment period, and in 7.1% (1 of 14) of the subjects during the washout period.

The majority of TEAEs were mild. Four subjects reported moderate TEAEs: three subjects during treatment with mifepristone alone (1 each reporting hypertension, rash, and vomiting) and 1 subject during treatment with mifepristone/ketoconazole (headache). All four moderate AEs were considered possibly or probably related to mifepristone treatment. Only 1 of the moderate AEs was considered to be possibly related to ketoconazole treatment. No severe TEAEs were reported.

Three subjects had elevated laboratory test results that were reported as drug-related TEAEs. Mildly elevated liver enzymes were noted for one subject starting on the morning of Day 14, and mildly elevated creatinine levels were noted for two subjects starting on the morning of Day 14. Dosing was not interrupted for any of the subjects, and the events resolved without sequelae.

No clinically significant effects of multiple-dose mifepristone treatment with or without multiple-dose ketoconazole treatment were observed on hematology or urinalysis parameters, vital signs, or ECGs.

## Example 4

The treatment regimen of a patient suffering from excess cortisol, who is receiving treatment with mifepristone at a daily dose of 1200 mg mifepristone, is altered to include concomitant administration of an effective amount of ketoconazole and a reduced daily dose of mifepristone, where the reduced daily dose of mifepristone is 900 mg, so that the patient receives concomitant administration of ketoconazole and mifepristone. A measurement indicates that the liver function of the patient is not significantly compromised by the concomitant administration of ketoconazole and the reduced dose of mifepristone.

## Example 5

The treatment regimen of a patient suffering from excess cortisol, who is receiving treatment with mifepristone at a daily dose of 900 mg mifepristone, is altered to include concomitant administration of an effective amount of ketoconazole and a reduced daily dose of mifepristone, where the reduced daily dose of mifepristone is 600 mg, so that the patient receives concomitant administration of ketoconazole and mifepristone. A measurement indicates that the liver function of the patient is not significantly compromised by the concomitant administration of ketoconazole and the reduced dose of mifepristone.

## Example 6

The treatment regimen of a patient suffering from excess cortisol, who is receiving treatment with mifepristone at a daily dose of 600 mg mifepristone, is altered to include concomitant administration of an effective amount of ketoconazole and a reduced daily dose of mifepristone, where the reduced daily dose of mifepristone is 300 mg, so that the patient receives concomitant administration of ketoconazole and mifepristone. A measurement indicates that the liver function of the patient is not significantly compromised by the concomitant administration of ketoconazole and the reduced dose of mifepristone.

## Example 7

The treatment regimen of a patient suffering from excess cortisol, who is receiving treatment with mifepristone at a daily dose of 1500 mg mifepristone, is altered to include concomitant administration of an effective amount of ketoconazole and a reduced daily dose of mifepristone, where the reduced daily dose of mifepristone is 1200 mg, so that the patient receives concomitant administration of ketoconazole and mifepristone. A measurement indicates that the liver function of the patient is not significantly compromised by the concomitant administration of ketoconazole and the reduced dose of mifepristone.

All patents, patent applications, and publications identified herein are hereby incorporated by reference herein in their entireties.

TABLE 1

| Product ID/ Batch No. (NME) | Study Objective | Study Design | No. Subjects Enter/ Complete (M/F) | Age: Mean Range | Treatments: Substrate | Treatments: Interacting Drug |
|---|---|---|---|---|---|---|
| Mifepristone 300 mg Tablet | Effect of ketoconazole 400 mg OD (or 200 mg BID) on PK of 300 | Phase 1, open-label, parallel group, single MIFE dose, | 12/12 (12 M) | 28 20-44 | MIFE 300 mg C1 | 400 mg/d Keto 400 mg OD |

TABLE 1-continued

| | | | | | | |
|---|---|---|---|---|---|---|
| Keto 200 mg Tablet | mg single dose Mifepristone given fasted | multiple keto doses, in healthy subjects | | | MIFE 300 mg C2 | 400 mg/d Keto 200 mg BID |

| | Product ID/ Batch No. (NME) | MIFEPRISTONE Mean PK Parameters (SD) $C_{max}$ ng/mL | $T_{max}$ h | $AUC_{tot}$ ng · h/mL | $AUC_t$ ng · h/mL | $T_{1/2}$ h | Mean Ratio Confidence Interval $C_{max}$ ng/mL | $AUC_{total}$ ng · h/mL |
|---|---|---|---|---|---|---|---|---|
| | Mifepristone 300 mg Tablet | 3398 (6.77) | median 2.00 | 116939 (26850) | 38111 (8768) | 37.1 (9.77) | 1.15 0.81-1.63 (C2/C1) | 1.05 0.72-1.54 (C2/C1) |
| | Keto 200 mg Tablet | 4143 (1736) | median 1.00 | 130925 (60942) | 40625 (16524) | 37.4 (18.5) | | |

MIFE = mifepristone,
Keto = ketoconazole,
$AUC_{tot}$ = $AUC_{total}$,
$AUC_\tau$ = $AUC_{0\text{-}24}$ hours following single dose of MIFE
C1 = Cohort 1,
C2 = Cohort 2

TABLE 2

| Product ID/ Batch # (NME) | Study Objective | Study Design | # Subjects Enter/ Complete (M/F) | Age: Mean Range | Treatments Substrate | Interacting Drug |
|---|---|---|---|---|---|---|
| Mifepristone 300 mg Tablet Keto 200 mg Tablet | Effect of 400 mg single dose of ketoconazole on PK an 8 day regimen of 300 mg OD Mifepristone (or 600 mg OD Mifepristone) given with moderate fat (34%) breakfast | Phase 1, open-label, parallel group, crossover within group with multiple MIFE doses, and single keto dose, in healthy subjects | 12/10 (12 M) | 29.8 20-43 | MIFE 300 mg/d C1 Day 7 | |
| | | | | | MIFE 300 mg/d C1 Day 8 | 400 mg Keto single dose |
| | | | | | MIFE 600 mg/d C2 Day 7 | |
| | | | | | MIFE 600 mg/d C2 Day 8 | 400 mg Keto single dose |

| | Product ID/ Batch # (NME) | MIFEPRISTONE Mean PK Parameters (SD) $C_{max}$ ng/mL | $T_{max}$ h | $AUC_{tot}$ ng · h/mL | $AUC_t$ ng · h/mL | $T_{1/2}$ h | Mean Ratio Confidence Interval $C_{max}$ ng/mL | $AUC_t$ ng · h/mL |
|---|---|---|---|---|---|---|---|---|
| | Mifepristone 300 mg Tablet | 2700 (534) | median 3.0 | NC[a] | 37734 (11905) | | 1.19 0.93-1.53 C1 Day 8/ Day 7 | 1.25 0.88-1.76 C1 Day 8/ Day 7 |
| | Keto 200 mg Tablet | 3240 (760) | median 2.1 | NC[a] | 47357 (17239) | 84.9 (46.6) | 1.39 1.13-1.70 C2 Day 8/ Day 7 | 1.28 1.09-1.49 C2 Day 8/ Day 7 |
| | | 3818 (703) | median 4.0 | NC[a] | 54174 (7305) | | 1.42 1.13-1.78 Day 7 C2/C1 | 1.48 1.13-1.94 Day 7 C2/C1 |
| | | 5264 (795) | median 4.0 | NC[a] | 69112 (9077) | 96.2 (45.4) | 1.65 1.30-2.08 Day 8 C2/C1 | 1.52 1.14-2.02 Day 8 C2/C1 |

MIFE = mifepristone,
Keto = ketoconazole
C1 = Cohort 1,
C2 = Cohort 2
$AUC_\tau$ = AUC0-24 hours following Day 7 or Day 8 dose of MIFE
[a]$AUC_{tot}$ = $AUC_{total}$, not computed (NC) for multiple dosing

Effects of Co-Administration with Ketoconazole on Mifepristone and Metabolites

Test: Day 17-600 mg Mifepristone OD+200 mg Ketoconazole BID

Reference: Day 12-600 mg Mifepristone OD

TABLE 3

| Analyte | Parameter | N | Ratio % Test/Reference | Lower 90% CI | Upper 90% CI |
|---|---|---|---|---|---|
| Mifepristone | $C_{max}$ | 13 | 127.59 | 116.66 | 139.54 |
| | $AUC_{0-24}$ | 13 | 138.01 | 127.12 | 149.84 |
| RU 42633 | $C_{max}$ | 13 | 105.73 | 95.92 | 116.54 |
| | $AUC_{0-24}$ | 13 | 102.33 | 94.31 | 111.03 |
| RU 42698 | $C_{max}$ | 13 | 169.13 | 156.36 | 182.94 |
| | $AUC_{0-24}$ | 13 | 166.86 | 155.06 | 179.57 |
| RU 42848 | $C_{max}$ | 13 | 95.48 | 90.82 | 100.38 |
| | $AUC_{0-24}$ | 13 | 94.88 | 91.33 | 98.56 |

Effects of Co-Administration with Mifepristone on Ketoconazole

Test: Day 17-600 mg Mifepristone OD+200 mg Ketoconazole BID

Reference: Day −1-200 mg Ketoconazole Single Dose

TABLE 4

| Parameter | N | Ratio % Test/Reference | Lower 90% CI | Upper 90% CI |
|---|---|---|---|---|
| $C_{max}$ | 14 | 252.71 | 214.85 | 297.26 |
| AUC | 14 | 365.36 | 333.78 | 399.93 |

Cross-study Comparison of Exposure to Mifepristone and Metabolites

Test: Present Study Day 17-600 mg Mifepristone OD+200 mg Ketoconazole BID

Reference: Historic Study Day 7-1200 mg Mifepristone OD Alone

TABLE 5

| Analyte | Parameter | Ratio % Test/Ref | Lower 90% CI | Upper 90% CI |
|---|---|---|---|---|
| Mifepristone | $C_{max}$ | 84.64 | 72.92 | 98.23 |
| | $AUC_{0-24}$ | 87.27 | 74.72 | 101.94 |
| RU 42633 | $C_{max}$ | 96.31 | 80.83 | 114.75 |
| | $AUC_{0-24}$ | 91.34 | 76.95 | 108.43 |
| RU 42698 | $C_{max}$ | 116.55 | 97.47 | 139.38 |
| | $AUC_{0-24}$ | 118.18 | 97.90 | 142.66 |
| RU 42848 | $C_{max}$ | 82.45 | 70.31 | 96.70 |
| | $AUC_{0-24}$ | 81.43 | 69.71 | 95.11 |

All doses given within 30 minutes after typical (34%) fat meal

The invention claimed is:

**1**. A method of treating Cushing's syndrome in a patient who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone, comprising the steps of:

reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone,

administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient,

wherein said strong CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

**2**. The method of claim **1**, wherein said CYP3A inhibitor is ketoconazole.

**3**. The method of claim **1**, wherein said CYP3A inhibitor is itraconazole.

**4**. The method of claim **1**, wherein said CYP3A inhibitor is clarithromycin.

**5**. A method of treating symptoms associated with elevated cortisol levels in a patient who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone, comprising the steps of:

reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone,

administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient,

wherein said strong CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

**6**. The method of claim **5**, wherein said CYP3A inhibitor is itraconazole.

**7**. The method of claim **5**, wherein said CYP3A inhibitor is ketoconazole.

**8**. The method of claim **5**, wherein said CYP3A inhibitor is clarithromycin.

**9**. The method of claim **5**, wherein said CYP3A inhibitor is itraconazole.

**10**. A method of controlling hyperglycemia secondary to hypercortisolism in a patient with endogenous Cushing's syndrome who is taking an original once-daily dose of 1200 mg or 900 mg per day of mifepristone, comprising the steps of:

reducing the original once-daily dose to an adjusted once-daily dose of 600 mg mifepristone,

administering the adjusted once-daily dose of 600 mg mifepristone and a strong CYP3A inhibitor to the patient,

wherein said strong CYP3A inhibitor is selected from the group consisting of ketoconazole, itraconazole, nefazodone, ritonavir, nelfmavir, indinavir, boceprevir, clarithromycin, conivaptan, lopinavir, posaconazole, saquinavir, telaprevir, cobicistat, troleandomycin, tipranivir, paritaprevir and voriconazole.

**11**. The method of claim **10**, wherein said CYP3A inhibitor is ketoconazole.

**12**. The method of claim **10**, wherein said CYP3A inhibitor is itraconazole.

**13**. The method of claim **10**, wherein said CYP3A inhibitor is clarithromycin.

* * * * *

# EXHIBIT C

US009829495B2

(12) **United States Patent**
**Moraitis**

(10) **Patent No.: US 9,829,495 B2**
(45) **Date of Patent: Nov. 28, 2017**

(54) **METHOD FOR DIFFERENTIALLY DIAGNOSING ACTH-DEPENDENT CUSHING'S SYNDROME**

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(51) **Int. Cl.**

| | |
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(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

This invention provides for an improved method for differentially diagnosing ACTH-dependent Cushing's syndrome. Current practice for differentially diagnosing ectopic ACTH syndrome and Cushing's Disease measures relative ACTH concentrations from the inferior petrosal venous sinus compared to fluid obtained from a periphery venous sample. This is performed before and after administration of exogenous corticotropin releasing factor, or after administration of metyrapone. This invention uses glucocorticoid receptor antagonists to induce release of endogenous CRH which stimulates ACTH to increase in patients with ectopic ACTH syndrome but not in those with Cushing's Disease.

**18 Claims, No Drawings**

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# METHOD FOR DIFFERENTIALLY DIAGNOSING ACTH-DEPENDENT CUSHING'S SYNDROME

## CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims benefit of U.S. provisional application No. 62/204,723, filed Aug. 13, 2015, the entire content of which is hereby incorporated by reference.

## BACKGROUND OF THE INVENTION

Cortisol is a steroid produced by the adrenal glands and is used in the body to respond to physical and emotional stress and to maintain adequate energy supply and blood sugar levels. Cortisol production is highly regulated by the hypothalamic-pituitary-adrenal axis (HPA) through a complex set of direct influences and negative feedback interactions. In healthy individuals, insufficient cortisol in the bloodstream triggers the hypothalamus to release corticotropin-releasing hormone (CRH) which signals to the pituitary gland to release adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal glands to produce more cortisol. Excessive cortisol inhibits hypothalamus from producing CRH, thus inhibiting the pituitary gland from releasing ACTH, which in turn suppresses cortisol production. The HPA regulation also results in a diurnal rhythm of cortisol levels, reaching peaks in the morning and nadirs around midnight. Pathological conditions associated with the HPA can affect the diurnal rhythm of the cortisol and ACTH production and cause serious health problems.

The biologic effects of cortisol, including those caused by hypercortisolemia, can be modulated at the GR level using receptor modulators, such as agonists, partial agonists and antagonists. Several different classes of agents are able to block the physiologic effects of GR-agonist binding. These antagonists include compositions which, by binding to GR, block the ability of an agonist to effectively bind to and/or activate the GR. One such known GR antagonist, mifepristone, has been found to be an effective anti-glucocorticoid agent in humans (Bertagna (1984) J. Clin. Endocrinol. Metab. 59:25). Mifepristone binds to the GR with high affinity, with a dissociation constant ($K_d$) of $10^{-9}$ M (Cadepond (1997) Annu. Rev. Med. 48:129).

A variety of disease states are capable of being treated with glucocorticoid receptor modulators, including, e.g., mifepristone; glucocorticoid receptor modulators (e.g, glucocorticoid receptor antagonists) disclosed in U.S. Pat. No. 7,928,237 and in U.S. Pat. No. 8,461,172; glucocorticoid receptor modulators disclosed in U.S. Pat. No. 8,685,973; glucocorticoid receptor modulators disclosed in U.S. Patent Publication 2014/0038926 (now U.S. Pat. No. 8,859,774); and other glucocorticoid receptor modulators. Exemplary disease states include major psychotic depression, mild cognitive impairment, psychosis, dementia, hyperglycemia, stress disorders, antipsychotic induced weight gain, delirium, cognitive impairment in depressed patients, cognitive deterioration in individuals with Down's syndrome, psychosis associated with interferon-alpha therapy, chronic pain (e.g. pain associate with gastroesophageal reflux disease), postpartum psychosis, postpartum depression, neurological disorders in premature infants, migraine headaches, obesity, diabetes, cardiovascular disease, hypertension, Syndrome X, depression, anxiety, glaucoma, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), neurodegeneration (e.g. Alzheimer's disease and Parkinson's disease), cognition enhancement, Cushing's Syndrome, Addison's Disease, osteoporosis, frailty, inflammatory diseases (e.g., osteoarthritis, rheumatoid arthritis, asthma and rhinitis), adrenal function-related ailments, viral infection, immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, multi-drug resistance, addiction, psychosis, anorexia, cachexia, post-traumatic stress syndrome post-surgical bone fracture, medical catabolism, and muscle frailty. The methods of treatment include administering to a patient in need of such treatment, a therapeutically effective amount of a glucocorticoid receptor modulator compound.



Cushing's syndrome is one of these problems. Patients having Cushing's syndrome usually have easy bruising; abdominal obesity and thin arms and legs; facial plethora; acne; proximal muscle weakness; and/or red purple stripes across the body. Cushing's syndrome is accompanied by hypercortisolemia, a condition involving a prolonged excess of circulating cortisol. Cushing's syndrome can be classified as exogenous Cushing's syndrome, which is caused by excess use of glucocorticoids drugs, such as prednisone, dexamethasone, and hydrocortisone, and endogenous Cushing's syndrome, which is caused by deregulatory abnormalities in the HPA axis. Endogenous Cushing's syndrome consists of the ACTH-independent Cushing's syndrome, characterized by an overproduction of cortisol in the absence of elevation of ACTH secretion; the ACTH-dependent Cushing's syndrome, characterized by excessive ACTH secretion.

ACTH-dependent Cushing's syndrome includes roughly 80% of patients having endogenous Cushing's syndrome and consists of two major forms: Cushing Disease and ectopic ACTH syndrome. The former is caused by a pituitary tumor and the latter is caused by a tumor outside the pituitary. Correct differential diagnosis between the Cushing Disease and ectopic ACTH syndrome is important for endocrinologists to recommend transphenoidal surgery or appropriate imaging to identify source of the ectopic ACTH secretion.

One current approach of differentially diagnosing patients with ACTH-dependent Cushing's syndrome involves measuring ACTH levels from samples obtained simultaneously from both inferior petrosal venous sinus (IPS)—a procedure referred to as inferior petrosal venous sinus sampling (IPSS)—and from the internal jugular or another peripheral vein. In one approach, referred herein as CRH-IPSS, 5 blood samples are taken from each IPS and the internal jugular vein, two before and three after administration of CRH. A central-to-periphery ACTH ratio of >2 before and >3 after the administration of CRH is consistent with Cushing Disease while a lower ratio favors ectopic ACTH syndrome. This procedure requires prolonged catheterization with the likelihood of infection, thrombosis, or bleeding rising with the duration of catheterization. In addition CRH is a protein which is expensive to produce, causing a shortage in supply between 2011 and early 2013, and requires sophisticated handling. Thus, the results from CRH-IPSS for differentially diagnosing patients with ACTH-dependent Cushing's syndrome often fall in the gray area. Desmopressin acetate (DDAVP), the alternative to CRH, which has also been used for IPSS, has similar disadvantages.

Another approach, referred to herein as metyrapone-IPSS, is similar to the one above, except that metyrapone instead of CRH is administered to the patient before IPSS and that samples are only taken from the patients after the metyrapone administration. Although metyrapone-IPSS improves the CRH-IPSS—since it dispenses with the need

for sampling before the administration of metyrapone, and thus reduces the duration of catheterization and likelihood of infection, thrombis, or bleeding associated therewith—it also has serious limitations. First, metyrapone acts to block the conversion of 11-deoxycortisol to cortisol by 11β-hydroxylase, causing a decrease in cortisol level, which in turn stimulates ACTH production and release. Since its effect on the ACTH secretion is indirect, the test result may be skewed by other factors affecting the cortisol synthesis. Second, as a cortisol synthesis blocker, treatment of metyrapone—especially at a high dose—may result in adrenal insufficiency or have deleterious effects on various normal bodily functions that require cortisol—for example, the anti-stress and anti-inflammation functions. Third, metyrapone is currently not available in the United States, consequently this diagnosis method is out of reach for many patients in this country.

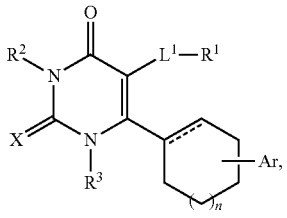
## BRIEF SUMMARY OF THE INVENTION

In one aspect, provided herein is a method of differentially diagnosing adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient with hypercortisolemia where the differential diagnosis is between ectopic ACTH syndrome and Cushing Disease. The method comprises: (i) selecting a patient with Cushing's syndrome and elevated ACTH levels; (ii) administering a dose of glucocorticoid receptor antagonist (GRA) sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal HPA function; (iii) waiting for at least two hours; and (iv) obtaining from the patient an ACTH concentration ratio, which is derived both from the ACTH concentrations in fluid obtained from either the left or right inferior petrosal venous sinus and from fluid obtained from a periphery vein, e.g., a jugular vein. The patient is diagnosed with Cushing Disease if the ACTH concentration ratio is greater than 3.

In some embodiments, the periphery venous sample is a jugular venous sample. In some embodiments, the ratio is derived from the ACTH concentration in fluid obtained from the left and right inferior petrosal venous sinuses. In some embodiments, the GRA is a selective inhibitor of the glucocorticoid receptor. In some cases, the first and second samplings of ACTH are taken 5-10 minutes apart from both the inferior petrosal venous sinus and a periphery venous sample.

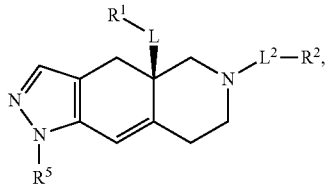
In some cases, the GRA is a selective inhibitor of the glucocorticoid receptor. In some embodiments, the GRA comprises a steroidal backbone with at least one phenyl-containing moiety in the 11-β position of the steroidal backbone. In some cases, the phenyl-containing moiety in the 11-β position of the steroidal backbone is a dimethylaminophenyl moiety. In some cases, the GRA is mifepristone. In some embodiments, the GRA is selected from the group consisting of 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9 estradien-3-one and (17α)-17-hydroxy-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one. In some embodiments, the glucocorticoid receptor antagonist is (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one.

In some embodiments, the GRA has a non-steroidal backbone. In some cases, the GRA backbone is a cyclohexyl pyrimidine. In some cases, wherein the cyclohexyl pyrimidine has the following formula:

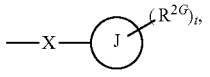


the dashed line is absent or a bond; X is selected from the group consisting of O and S; $R^1$ is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, optionally substituted with 1-3 $R^{1a}$ groups; each $R^{1a}$ is independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl $OR^{1b}$, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloaloxy, $OR^{1b}$, $NR^{1b}R^{1c}$, $C(O)R^{1b}$, $C(O)OR^{1b}$, $OC(O)R^{1b}$, $C(O)NR^{1b}R^{1c}$, $NR^{1b}C(O)R^{1c}$, $S_2R^{1b}$, $SO_2NR^{1b}R^{1c}$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl; $R^{1b}$ and $R^{1c}$ are each independently selected from the group consisting of H and $C_{1-6}$ alkyl; $R^2$ is selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{1-6}$ alkyl-$OR^{1b}$, $C_{1-6}$ alkyl $NR^{1b}R^{1c}$ and $C_{1-6}$ alkylene heterocycloalkyl; $R^3$ is selected from the group consisting of H and $C_{1-6}$ alkyl; Ar is aryl, optionally substituted with 1-4 $R^4$ groups; each $R^4$ is independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $C_{1-6}$ haloalkyl, and $C_{1-6}$ haloalkoxy; $L^1$ is a bond or $C_{1-6}$ alkylene; and subscript n is an integer from 0 to 3, or salts and isomers thereof.

In some cases, the GRA backbone is a fused azadecalin. In some cases, the fused azadecalin is a compound having the following formula:



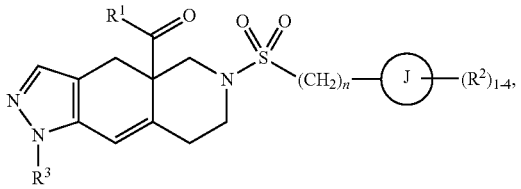
wherein $L^1$ and $L^2$ are members independently selected from a bond and unsubstituted alkylene; $R^1$ is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, —$OR^{1A}$, $NR^{1C}R^{1D}$, —C(O)$NR^{1C}R^{1D}$, and —C(O)$OR^{1A}$, wherein $R^{1A}$ is a member selected from hydrogen, unsubstituted alkyl, and unsubstituted heteroalkyl; $R^{1C}$ and $R^{1D}$ are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl, and are optionally joined to form an unsubstituted ring with the nitrogen to which they are attached, wherein said ring optionally comprises an additional ring nitrogen. $R^2$ has the formula:



wherein $R^{2G}$ is a member selected from hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, —CN, and —$CF_3$; J is phenyl; t is an integer from 0 to 5; X is

—$S(O_2)$—; and $R^5$ is phenyl optionally substituted with 1-5 $R^{5A}$ groups, wherein $R^{5A}$ is a member selected from hydrogen, halogen, —$OR^{5A1}$, $S(O_2)NR^{5A2}R^{5A3}$, —CN, and unsubstituted alkyl, and $R^{5A1}$ is a member selected from hydrogen and unsubstituted alkyl, and $R^{5A2}$ and $R^{5A3}$ are members independently selected from hydrogen and unsubstituted alkyl, or salts and isomers thereof.

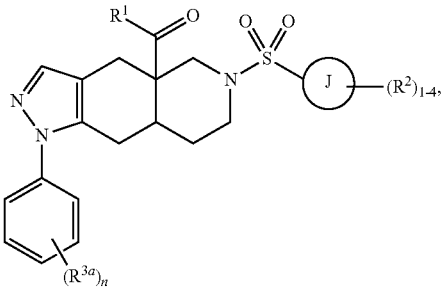
In some cases, the GRA backbone is a heteroaryl ketone fused azadecalin or an octahydro fused azadecalin. In some cases, the heteroaryl ketone fused azadecalin has the formula:



wherein $R^1$ is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from $R^{1a}$; each $R^{1a}$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, CN, N-oxide, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl; ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring, and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O, and S; each $R^2$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_1$ 6 haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, $C_{1-6}$ alkyl-$C_{1-6}$ alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, $SR^{2a}$, $S(O)R^{2a}$, $S(O)_2R^{2a}$, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 $R^{2c}$ groups; alternatively, two $R^2$ groups linked to the same carbon are combined to form an oxo group (=O); alternatively, two $R^2$ groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O, and S, wherein the heterocycloalkyl ring is optionally substituted with 1-3 $R^{2d}$ groups; $R^{2a}$ and $R^{2b}$ are each independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl; each $R^{2c}$ is independently selected from the group consisting of hydrogen, halogen, hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, CN, and $NR^{2a}R^{2b}$; each $R^{2d}$ is independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl, or two $R^{2d}$ groups attached to the same ring atom are combined to form (=O); $R^3$ is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 $R^{3a}$ groups; each $R^{3a}$ is independently selected from the group consisting of hydrogen, halogen, and $C_{1-6}$ haloalkyl; and subscript n is an integer from 0 to 3; or salts and isomers thereof.

In some cases, the octahydro fused azadecalin has the formula:





wherein $R^1$ is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O, and S, optionally substituted with 1-4 groups each independently selected from $R^{1a}$; each $R^{1a}$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, N-oxide, and $C_{3-8}$ cycloalkyl; ring J is selected from the group consisting of an aryl ring and a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O, and S; each $R^2$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, $C_{1-6}$ alkyl-$C_{1-6}$ alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, $SR^{2a}$, $S(O)R^{2a}$, $S(O)_2R^{2a}$, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl having from 1 to 3 heteroatoms each independently selected from the group consisting of N, O, and S; alternatively, the two $R^2$ groups on adjacent ring atoms are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O, and S, wherein the heterocycloalkyl ring is optionally substituted with 1-3 $R^{2c}$ groups; $R^{2a}$, $R^{2b}$, and $R^{2c}$ are each independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl; each $R^{3a}$ is independently halogen; and subscript n is an integer from 0 to 3, or salts and isomers thereof.

In yet another aspect, provided herein is a diagnostic composition, or a diagnostic kit comprising a glucocorticoid receptor antagonist (GRA) for use in a method of differentially diagnosing adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient where the differential diagnosis is between ectopic ACTH syndrome and Cushing Disease, the method comprising the step of determining the ACTH concentration ratio from a patient with Cushing's syndrome and an elevated ACTH level, where the patient has been administered a dose of glucocorticoid receptor antagonist (GRA) at least two hours prior to the removal of venous samples and where the amount of GRA administered to the patient is sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function; wherein the ACTH concentration ratio is derived from the ACTH concentrations in fluid obtained from either the left or right inferior petrosal venous sinus and from fluid obtained from a periphery venous sample; and wherein an ACTH concentration ratio of greater than 3 for the ACTH concentration from the inferior venous sinus sample over the periphery venous sinus sample is diagnostic indicative of Cushing's disease.

In yet another aspect, provided here in is a method of obtaining a measurement indicative of differential diagnosis of adrenocorticotropic hormone (ACTH)-dependent Cush-

ing's syndrome in a patient where the differential diagnosis is between ectopic ACTH syndrome and Cushing Disease, the method comprising the step of: (i) determining the ACTH concentration ratio from a patient with Cushing's syndrome and an elevated ACTH level, where the patient has been administered a dose of glucocorticoid receptor antagonist (GRA) at least two hours prior to the removal of venous samples and where the amount of GRA administered to the patient is sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function; wherein the ACTH concentration ratio is derived from the ACTH concentrations in fluid obtained from either the left or right inferior petrosal venous sinus and from fluid obtained from a periphery venous sample; and wherein an ACTH concentration ratio of greater than 3 for the ACTH concentration from the inferior venous sinus sample over the periphery venous sinus sample is indicative of Cushing's disease.

In yet another aspect, provided herein is a glucocorticoid receptor antagonist (GRA) for use in a method of differentially diagnosing adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient where the differential diagnosis is between ectopic ACTH syndrome and Cushing Disease, the method comprising the steps of: (i) selecting a patient with Cushing's syndrome and also elevated ACTH levels; (ii) administering a dose of the GRA sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function; (iii) waiting for at least two hours; and (iv) obtaining from the patient an ACTH concentration ratio wherein the ratio is derived from the ACTH concentrations in fluid obtained from either the left or right inferior petrosal venous sinus and from fluid obtained from a periphery venous sample; wherein an ACTH concentration ratio of greater than 3 for the ACTH concentration from the inferior venous sinus sample over the periphery venous sinus sample is diagnostic of Cushing's disease.

Other objects, features, and advantages of the present invention will be apparent to one of skill in the art from the following detailed description and figures.

## DETAILED DESCRIPTION OF THE INVENTION

### I. Introduction

This invention involves the use of GRAs to provide a robust and reproducible means to stimulate ACTH production in the pituitary gland for the differential diagnosis of patients with ACTH-dependent Cushing's syndrome, where the differential diagnosis is between ectopic ACTH syndrome and Cushing Disease. GRAs are first administered, and blood samples are then taken by IPSS after sufficient time for the assessment of ACTH levels.

The claimed methods have many advantages over the existing differential diagnosis methods, such as CRH-IPSS, DDAVP-IPSS and metyrapone-IPSS. First, the claimed methods are more robust compared to metyrapone-IPSS. GRAs used in the invention act to block cortisol binding to the receptor—thus preventing cortisol from inhibiting ACTH production and resulting in increased ACTH production/secretion. Compared to metyrapone, which acts to block the cortisol synthesis pathway, GRAs' effect on ACTH stimulation is more direct, thus making the test results more reliable. Second, compared to CRH/DDAVP-IPSS, the methods are cost-effective and convenient to use because GRAs are orally deliverable and less expensive than CRH to manufacture and store. Third, compared to CRH/DDAVP-IPSS, the method disclosed herein dispenses with the need to sample blood before the administration of GRAs, and thus reduces the duration of catheterization and minimizes complications associated with prolonged catheterization.

### II. Definitions

The term "endogenous Cushing's syndrome" refers to a form of Cushing's syndrome, where the excess cortisol level is caused by the body's own overproduction of corti sol.

The term "Adrenocorticotropic hormone (ACTH)-dependent Cushings syndrome" refers to a form of endogenous Cushing's syndrome, which is caused by abnormal production of ACTH. There are two major forms of ACTH-dependent Cushing's syndrome: Cushing Disease (accounting for about 80% of the cases) and ectopic ACTH syndrome (accounting for 20% of the cases).

The term "ACTH concentration ratio", "ACTH ratio", "pituitary to periphery ACTH ratio", or "central to periphery ACTH ratio" disclosed herein refers to the ratio between the amount, level, or concentration of ACTH in the blood sample obtained from inferior petrosal sinus and the blood sample obtained from the periphery veins. In one embodiment, the periphery vein is the jugular vein.

The term "prolactin concentration ratio", "prolactin ratio", "pituitary to periphery prolactin ratio", or "central to periphery prolactin ratio" disclosed herein refers to the ratio between the amount, level, or concentration of prolactin in the blood sample obtained from inferior petrosal sinus and the blood sample obtained from the periphery veins. In one embodiment, the periphery vein is the jugular vein.

The term "differentially diagnosing" refers to the distinguishing of a particular disease or condition from others that present similar symptoms. A differential diagnostic method is a systematic diagnostic method used to identify the presence of a condition where multiple alternatives are possible. This method is essentially a process of elimination or a process of obtaining information that shrinks the "probabilities" of candidate conditions to negligible levels. The method uses evidence such as symptoms, test results, patient history, and medical knowledge to adjust epistemic confidences in the mind of the diagnostician (or, for computerized or computer-assisted diagnosis, the software of the system). Often each individual option of a possible disease is called a differential diagnosis.

The term "ectopic ACTH syndrome" refers to the abnormal production of ACTH due to ectopic ACTH secretion by an extrapituitary tumor. These extrapituitary tumors frequently originate in lungs, but in some cases originate from the thymus, pancreas, adrenal gland or thyroid.

The term "Cushing Disease" refers to the condition in which the pituitary gland releases too much ACTH as a result of a tumor located in—or excess growth (hyperplasia) of—the pituitary gland. Cushing Disease is a form of Cushing's syndrome.

The term "hypercortisolemia" refers a condition of having a higher than normal amount of circulating cortisol.

The term "inferior petrosal sinus sampling (IPSS)" refers to an invasive procedure performed to obtain blood samples from one or both petrosal venous sinuses by inserting catheters in one or both inferior petrosal veins via the jugular or femoral veins. The petrosal venous sinus drains the pituitary via the cavernous sinus. Thus, samples obtained from IPSS are often analyzed and compared with the

samples obtained from periphery blood for the amount of a particular analyte to detect signs of a disease relating to the pituitary gland.

The term "jugular venous sampling" refers to an invasive procedure performed to obtain blood samples from jugular veins (a periphery vein) by inserting catheters in the internal jugular vein via femoral veins. The tips of the catheters are typically advanced to the level of the angles of the mandible.

The term "periphery venous sinus sampling" refers to an invasive procedure performed to obtain blood samples from periphery veins by catheterization. Non-limiting examples of periphery veins include adrenal veins, high inferior vena cava, hepatic vein, azygos and hemiazygos veins, right atrium, right and left innominate and thymic veins, jugular veins, and both superior and middle thyroid veins.

The term "patient," "individual", or "subject" is used interchangeably to refer to a human subject. In some cases, the individual is suspected of having Cushing's Syndrome.

The term "administering" includes oral administration, topical contact, administration as a suppository, intravenous, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal, or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, epicutaneous, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, and transdermal patches.

The term "sample" refers to a biological sample obtained from a human subject. The sample can be any cell, tissue or fluid from a human subject. Samples can be subject to various treatment, storage or processing procedures before being analyzed according to the methods described herein. Generally, the terms "sample" or "samples" are not intended to be limited by their source, origin, manner of procurement, treatment, processing, storage or analysis, or any modification.

The term "cortisol" refers to a glucocorticoid hormone that is produced by the zona fasciculata of the adrenal gland.

The term "adrenocorticotropic hormone" or "ACTH" refers to a polypeptide-based hormone that is normally produced and secreted by the anterior pituitary gland. ACTH stimulates secretion of cortisol and other glucocorticoids (GCs) by specialized cells of the adrenal cortex. In healthy mammals, ACTH secretion is tightly regulated. ACTH secretion is positively regulated by corticotropin releasing hormone (CRH), which is released by the hypothalamus. ACTH secretion is negatively regulated by cortisol and other glucocorticoids.

The term "measuring the level," in the context of cortisol, ACTH, or other steroids, refers determining, detecting, or quantitating the amount, level, or concentration of, for example, cortisol, ACTH or other steroids in a sample obtained from a subject.

The term a "increase" or a "decrease" refers to a detectable positive or negative change in quantity from a comparison control, e.g., an established standard control (such as an average level of cortisol in a normal, healthy subject who does not have hypercortisolemia). An increase is a positive change that is typically at least 5%, at least 10%, or at least 20%, or 50%, or 100%, and can be as high as at least 1.5-fold, at least 2-fold, at least 5-fold, or even 10-fold of the control value. Similarly, a decrease is a negative change that is typically at least 5%, at least 10%, or at least 20%, 30%, or 50%, or even as high as at least 80% or 90% of the control value. Other terms indicating quantitative changes or differences from a comparative basis, such as "more," "less," "higher," and "lower," are used in this application in the same fashion as described above.

The term "normal reference value", "reference value", or "standard control level" refers to the a predetermined amount, level, or concentration of a particular analyte, e.g., ACTH, cortisol, or prolactin—by comparison to which a diagnosis of the presence or absence of a particular condition can be made, e.g., hypercortisolemia. Normal reference values referred to in this disclosure are in some cases provided by the commercial test that is used to determine the analyte levels. In some cases, a normal reference value, reference value, or standard control level is established as the average of the amount, level, or concentration of an analyte from one or more normal, healthy subjects, e.g., subjects who have normal HPA function. In some cases, they are established as a range of the level, amount, or concentration of the analyte in a group of healthy subjects. Normal reference values may vary depending on the nature of the sample, the manner or timing of sample collection, as well as other factors such as the sex, age, and ethnicity of the subjects for whom such a control value is established.

The term "elevated level", "elevated amount", or "elevated concentration" refers to the level or amount of the analyte that is higher than the normal reference value for that analyte.

The term "chromatography" refers to a process in which a chemical mixture carried by a liquid or gas is separated into components as a result of the differential distribution of the chemical entities as they flow around or over a stationary liquid or solid phase.

The term "liquid chromatography" or "LC" refers to a process of selective retardation of one or more components of a fluid solution when the fluid uniformly percolates either through a column of a finely divided substance or through capillary passageways. The retardation results from the distribution of the components of the mixture between one or more stationary phases and the bulk fluid, (i.e., mobile phase), as this fluid moves relative to the stationary phase(s). Examples of "liquid chromatography" include reverse phase liquid chromatography (RPLC), high performance liquid chromatography (HPLC), and turbulent flow liquid chromatography (TFLC) (sometimes known as high turbulence liquid chromatography (HTLC) or high throughput liquid chromatography).

The term "high performance liquid chromatography" or "HPLC" (also sometimes known as "high pressure liquid chromatography") refers to liquid chromatography in which the degree of separation is increased by forcing the mobile phase under pressure through a stationary phase—typically a densely packed column. As used herein, the term "ultra high performance liquid chromatography", "HPLC" or "UHPLC" (sometimes known as "ultra high pressure liquid chromatography") refers to HPLC which occurs at much higher pressures than in traditional HPLC techniques.

The term "glucocorticosteroid" ("GC") or "glucocorticoid" refers to a steroid hormone that binds to a glucocorticoid receptor. Glucocorticosteroids are typically characterized by having 21 carbon atoms, an $\alpha,\beta$-unsaturated ketone in ring A, and an $\alpha$-ketol group attached to ring D. They differ in the extent of oxygenation or hydroxylation at C-11, C-17, and C-19; see Rawn, "Biosynthesis and Transport of Membrane Lipids and Formation of Cholesterol Derivatives," in Biochemistry, Daisy et al. (eds.), 1989, pg. 567.

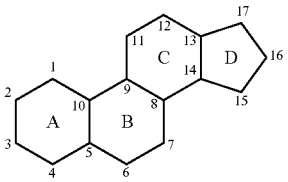
The term "glucocorticoid receptor" ("GR") refers to the type II GR which specifically binds to cortisol and/or cortisol analogs such as dexamethasone; See, e.g., Turner & Muller, *J Mol. Endocrinol,* 2005 (35): 283-292. The GR is also referred to as the cortisol receptor. The term includes isoforms of GR, recombinant GR and mutated GR. Inhibition constants ($K_i$) against the human GR receptor type II (Genbank: P04150) are between 0.0001 nM and 1,000 nM; preferably between 0.0005 nM and 10 nM, and most preferably between 0.001 nM and 1 nM.

The term "glucocorticoid receptor antagonist" or "GRA" refers to any composition or compound which partially or completely inhibits (antagonizes) the binding of a glucocorticoid receptor (GR) agonist, such as cortisol, or cortisol analogs, synthetic or natural, to a GR. A "specific glucocorticoid receptor antagonist" refers to any composition or compound which inhibits any biological response associated with the binding of a GR to an agonist. By "specific," the drug preferentially binds to the GR rather than to other nuclear receptors, such as the mineralocorticoid receptor (MR), androgen receptor (AR), or progesterone receptor (PR). It is preferred that the specific glucocorticoid receptor antagonist binds GR with an affinity that is 10× greater ($1/10^{th}$ the $K_d$ value) than its affinity to the MR, AR, or PR, both the MR and PR, both the MR and AR, both the AR and PR, or to the MR, AR, and PR. In a more preferred embodiment, the specific glucocorticoid receptor antagonist binds a GR with an affinity that is 100× greater ($1/100^{th}$ the $K_d$ value) than its affinity to the MR, AR, or PR, both the MR and PR, both the MR and AR, both the AR and PR, or to the MR, AR, and PR.

The term "selective inhibitor" in the context of a glucocorticoid receptor refers to a chemical compound that selectively interferes with the binding of a specific glucocorticoid receptor agonist and a glucocorticoid receptor.

The term "steroidal backbone" in the context of glucocorticoid receptor antagonists containing such refers to glucocorticoid receptor antagonists that contain modifications of the basic structure of cortisol, an endogenous steroidal glucocorticoid receptor ligand. The basic structure of a steroidal backbone is provided as Formula I:

Formula I




Steroidal Backbone

The two most commonly known classes of structural modifications of the cortisol steroid backbone to create glucocorticoid antagonists include modifications of the 11-β hydroxy group and modification of the 17-0 side chain (See, e. g., Lefebvre (1989) J. Steroid Biochem. 33: 557-563).

As used herein, the term "non-steroidal backbone" in the context of glucocorticoid receptor antagonists containing such refers to glucocorticoid receptor antagonists that do not share structural homology to, or are not modifications of, cortisol. Such compounds include synthetic mimetics and analogs of proteins, including partially peptidic, pseudopeptidic, and non-peptidic molecular entities.

Non-steroidal GRA compounds also include glucocorticoid receptor antagonists having a cyclohexyl-pyrimidine backbone, a fused azadecalin backbone, a heteroaryl ketone fused azadecalin backbone, or an octahydro fused azadecalin backbone. Exemplary glucocorticoid receptor antagonists having a cyclohexyl-pyrimidine backbone include those described in U.S. Pat. No. 8,685,973. Exemplary GRAs having a fused azadecalin backbone include those described in U.S. Pat. Nos. 7,928,237 and 8,461,172. Exemplary GRAs having a heteroaryl ketone fused azadecalin backbone include those described in U.S. Pat. Pub. 2014/0038926. Exemplary GRAs having an octohydro fused azadecalin backbone include those described in U.S. Provisional Patent Appl. No. 61/908,333, entitled Octahydro Fused Azadecalin Glucocorticoid Receptor Modulators, filed on Nov. 25, 2013.

Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., —$CH_2O$— is equivalent to —$OCH_2$—.

"Alkyl" refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons, such as $C_{1-2}$, $C_{1-3}$, $C_{1-4}$, $C_{1-5}$, $C_{1-6}$, $C_{1-7}$, $C_{1-8}$, $C_{1-9}$, $C_{1-10}$, $C_{2-3}$, $C_{2-4}$, $C_{2-5}$, $C_{2-6}$, $C_{3-4}$, $C_{3-5}$, $C_{3-6}$, $C_{4-5}$, $C_{4-6}$, and $C_{5-6}$. For example, $C_{1-6}$ alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec.butyl, tert.butyl, pentyl, isopentyl, and hexyl.

"Alkoxy" refers to an alkyl group having an oxygen atom that connects the alkyl group to the point of attachment: alkyl-O—. As for the alkyl group, alkoxy groups can have any suitable number of carbon atoms, such as $C_{1-6}$. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, iso-propoxy, butoxy, 2-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, pentoxy, hexoxy, etc.

"Halogen" refers to fluorine, chlorine, bromine, and iodine.

"Haloalkyl" refers to alkyl, as defined above, where some or all of the hydrogen atoms are replaced with halogen atoms. As for the alkyl group, haloalkyl groups can have any suitable number of carbon atoms, such as $C_{1-6}$, and include trifluoromethyl, fluoromethyl, etc.

The term "perfluoro" can be used to define a compound or radical where all the hydrogens are replaced with fluorine. For example, perfluoromethane includes 1,1,1-trifluoromethyl.

"Haloalkoxy" refers to an alkoxy group where some or all of the hydrogen atoms are substituted with halogen atoms. As for the alkyl group, haloalkoxy groups can have any suitable number of carbon atoms, such as $C_{1-6}$. The alkoxy groups can be substituted with 1, 2, 3, or more halogens. When all the hydrogens are replaced with a halogen, for example by fluorine, the compounds are per-substituted, for example, perfluorinated. Haloalkoxy includes, but is not limited to, trifluoromethoxy, 2,2,2,-trifluoroethoxy, and perfluoroethoxy.

"Cycloalkyl" refers to a saturated or partially unsaturated, monocyclic, fused bicyclic, or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated. Cycloalkyl can include any number of carbons, such as $C_{3-6}$, $C_{4-6}$, $C_{5-6}$, $C_{3-8}$, $C_{4-8}$, $C_{5-8}$, $C_{6-8}$, $C_{3-9}$, $C_{3-10}$, $C_{3-11}$, and $C_{3-12}$. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic cycloalkyl rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene, and adamantane. Cycloalkyl groups can also be partially unsaturated, having one or more double or triple bonds in the ring.

Representative cycloalkyl groups that are partially unsaturated include, but are not limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene. When cycloalkyl is a saturated monocyclic $C_{3-8}$ cycloalkyl, exemplary groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. When cycloalkyl is a saturated monocyclic $C_{3-6}$ cycloalkyl, exemplary groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

"Heterocycloalkyl" refers to a saturated ring system having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O, and S. Additional heteroatoms can also be useful, including but not limited to, B, Al, Si, and P. The heteroatoms can also be oxidized, such as, but not limited to, —S(O)— and —$S(O)_2$—. Heterocycloalkyl groups can include any number of ring atoms, such as 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heterocycloalkyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. The heterocycloalkyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxalidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. The heterocycloalkyl groups can also be fused to aromatic or non-aromatic ring systems to form members including, but not limited to, indoline.

When heterocycloalkyl includes 3 to 8 ring members and 1 to 3 heteroatoms, representative members include, but are not limited to, pyrrolidine, piperidine, tetrahydrofuran, oxane, tetrahydrothiophene, thiane, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, morpholine, thiomorpholine, dioxane and dithiane. Heterocycloalkyl can also form a ring having 5 to 6 ring members and 1 to 2 heteroatoms, with representative members including, but not limited to, pyrrolidine, piperidine, tetrahydrofuran, tetrahydrothiophene, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, and morpholine.

"Aryl" refers to an aromatic ring system having any suitable number of ring atoms and any suitable number of rings. Aryl groups can include any suitable number of ring atoms, such as 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 ring atoms, as well as from 6 to 10, 6 to 12, or 6 to 14 ring members. Aryl groups can be monocyclic, fused to form bicyclic or tricyclic groups, or linked by a bond to form a biaryl group. Representative aryl groups include phenyl, naphthyl and biphenyl. Other aryl groups include benzyl, that has a methylene linking group. Some aryl groups have from 6 to 12 ring members, such as phenyl, naphthyl, or biphenyl. Other aryl groups have from 6 to 10 ring members, such as phenyl or naphthyl. Some other aryl groups have 6 ring members, such as phenyl. Aryl groups can be substituted or unsubstituted.

"Heteroaryl" refers to a monocyclic, fused bicyclic, or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O, or S. Additional heteroatoms can also be useful, including but not limited to, B, Al, Si, and P. The heteroatoms can also be oxidized, such as, but not limited to, N-oxide, —S(O)—, and —$S(O)_2$—. Heteroaryl groups can include any number of ring atoms, such as 3 to 6, 4 to 6, 5 to 6, 3 to 8, 4 to 8, 5 to 8, 6 to 8, 3 to 9, 3 to 10, 3 to 11, or 3 to 12 ring members. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4, or 5; or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. Heteroaryl groups can have from 5 to 8 ring members and from 1 to 4 heteroatoms, or from 5 to 8 ring members and from 1 to 3 heteroatoms, or from 5 to 6 ring members and from 1 to 4 heteroatoms, or from 5 to 6 ring members and from 1 to 3 heteroatoms. The heteroaryl group can include groups such as pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4-, and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. The heteroaryl groups can also be fused to aromatic ring systems, such as a phenyl ring, to form members including, but not limited to, benzopyrroles such as indole and isoindole, benzopyridines such as quinoline and isoquinoline, benzopyrazine (quinoxaline), benzopyrimidine (quinazoline), benzopyridazines such as phthalazine and cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include heteroaryl rings linked by a bond, such as bipyridine. Heteroaryl groups can be substituted or unsubstituted.

The heteroaryl groups can be linked via any position on the ring. For example, pyrrole includes 1-, 2-, and 3-pyrrole; pyridine includes 2-, 3- and 4-pyridine; imidazole includes 1-, 2-, 4- and 5-imidazole; pyrazole includes 1-, 3-, 4- and 5-pyrazole; triazole includes 1-, 4- and 5-triazole; tetrazole includes 1- and 5-tetrazole; pyrimidine includes 2-, 4-, 5- and 6-pyrimidine; pyridazine includes 3- and 4-pyridazine; 1,2,3-triazine includes 4- and 5-triazine; 1,2,4-triazine includes 3-, 5- and 6-triazine; 1,3,5-triazine includes 2-triazine; thiophene includes 2- and 3-thiophene; furan includes 2- and 3-furan; thiazole includes 2-, 4- and 5-thiazole; isothiazole includes 3-, 4- and 5-isothiazole; oxazole includes 2-, 4- and 5-oxazole; isoxazole includes 3-, 4- and 5-isoxazole; indole includes 1-, 2- and 3-indole; isoindole includes 1- and 2-isoindole; quinoline includes 2-, 3- and 4-quinoline; isoquinoline includes 1-, 3- and 4-isoquinoline; quinazoline includes 2- and 4-quinoazoline; cinnoline includes 3- and 4-cinnoline; benzothiophene includes 2- and 3-benzothiophene; and benzofuran includes 2- and 3-benzofuran.

Some heteroaryl groups include those having from 5 to 10 ring members and from 1 to 3 ring atoms including N, O, or S, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include those having from 5 to 8 ring members and from 1 to 3 heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. Some other heteroaryl groups include those having from 9 to 12 ring members and from 1 to 3 heteroatoms, such as indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, benzofuran and bipyridine. Still other heteroaryl groups include those having from 5 to 6 ring members and from 1 to 2 ring heteroatoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, pyrazine, pyrimidine, pyridazine, thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole.

Some heteroaryl groups include from 5 to 10 ring members and only nitrogen heteroatoms, such as pyrrole, pyri-

dine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, and cinnoline. Other heteroaryl groups include from 5 to 10 ring members and only oxygen heteroatoms, such as furan and benzofuran. Some other heteroaryl groups include from 5 to 10 ring members and only sulfur heteroatoms, such as thiophene and benzothiophene. Still other heteroaryl groups include from 5 to 10 ring members and at least two heteroatoms, such as imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiazole, isothiazole, oxazole, isoxazole, quinoxaline, quinazoline, phthalazine, and cinnoline.

"Heteroatoms" refers to O, S, or N.

"Salt" refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of pharmaceutically-acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid, and the like) salts, and quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically-acceptable salts are non-toxic. Additional information on suitable pharmaceutically-acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

"Isomers" refers to compounds with the same chemical formula but which are structurally distinguishable.

"Tautomer" refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one form to another.

Descriptions of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to produce compounds which are not inherently unstable—and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions—such as aqueous, neutral, or physiological conditions.

"Pharmaceutically-acceptable excipient" and "pharmaceutically-acceptable carrier" refer to a substance that aids the administration of an active agent to—and absorption by—a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically-acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors, and the like. One of ordinary skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

## III. Detailed Descriptions of Embodiments

### A. Method for Differential Diagnosis of ACTH-Dependent Cushing's Syndrome

#### 1. Selecting Patients Having ACTH-Dependent Cushing's Syndrome

The methods disclosed herein is used to provide differential diagnosis between Cushing Disease and ectopic ACTH syndrome to patients who have already been diagnosed as having ACTH-dependent Cushing's syndrome. A diagnosis of ACTH-dependent Cushing's syndrome can be made based on observation of certain clinical symptoms, the detection of hypercortisolemia and elevated blood ACTH levels.

a. Clinical Symptoms

Eligible patients may exhibit one or more of the following symptoms: easy bruising; abdominal obesity and thin arms and legs; facial plethora; acne; proximal myopathy (or proximal muscle weakness); striae (especially if reddish purple and 1 cm wide); and thin skin. Patients may also frequently feel changes in mood; change in appetite, headaches; a chronic feeling of tiredness; osteoporosis; low potassium; diabetes, and high blood pressure; decreased concentration peripheral edema hypokalemia; decreased libido acne kidney stones; impaired memory (especially short term); and unusual infections. Females patients may have irregular menstruation, hirsutism, or female balding. Pediatric patients may have weight gain with decreasing growth velocity; abnormal genital virilization; short stature; and pseudoprecocious puberty or delayed puberty. The next step is to confirm these patients have hypercortisolemia.

b Hypercortisolemia

A diagnosis of hypercortisolemia requires the determination of the patient's circulating cortisol level. Various types of samples that can be used for this purpose, such as saliva, urine, whole blood, serum, and plasma. Samples may also be collected at different time during the day. In one approach, the patient's whole blood sample is collected and processed to collect serum, i.e., in the morning, e.g., at 8 am. or in the afternoon, e.g., at 4 pm. The collected serum sample is refrigerated or frozen within, e.g., 2 hours of collection. Analysis of the serum sample is performed in a timely fashion, e.g. within 7 days from sample collection. In another approach, the patient's cortisol levels are measured from his or her saliva samples. Salivary cortisol is in equilibrium with the free cortisol in blood circulation. Changes of cortisol levels in the bloodstream are paralleled, within minutes, by similar alterations in salivary cortisol concentrations, such that one can use the latter as a surrogate of the former. The commonly used saliva-based cortisol test is the midnight saliva test, which measures cortisol levels from saliva samples collected at between 11 pm and midnight. Intake of food or drink is prohibited at least 15 minutes prior to sample collection. Saliva samples are collected by keeping and rolling a swab in mouth for approximately 2 minutes. The saliva samples, ambient or refrigerated, are then sent to a laboratory for cortisol level determination in a timely fashion, e.g., within 7 days from sample collection.

Methods for measuring cortisol levels are known to those in the art. Useful assays include immunoassays, e.g., competitive immunoassay, radioimmunoassay, immunofluorometric enzyme assay, and ELISA, competitive protein-binding assay and mass spectrometry, e.g., high-performance liquid chromatography/triple quadrupole-mass spectrometry (LC-MS/MS). Commercial kits for measuring cortisol in samples are available from Beckman-Coulter, Seimens, Roche Diagnostics, and the like. Non-limiting examples of cortisol tests are Mayo Clinic's SALCT, CORT, CORTU, and CINP tests; an ADVIA Centaur® Cortisol assay (Siemens Healthcare Global); ARCHITECT i2000SR cortisol (Abbott); Immulite® 2000 Cortisol assay (Siemans Healthcare Global; #L2KCO2), Vitros ECi Cortisol assay (Ortho Clinical Diagnostics; #107 4053), and Elecsys® Cortisol Immunoassay (Roche Molecular Diagnostics; #11875116160).

The patient's cortisol measurement is then compared with the normal reference value; a level higher than the normal reference value indicates the patient has hypercortisolemia. The normal reference values for cortisol levels vary depending on the nature of the samples, the manner and timing of sample collection (higher for samples collected in the morning and lower for samples collected at night), and the detection method. Thus, it is essential to interpret test results in the context of the appropriate normal reference values. Various commercial kits provide the normal reference values in testing protocols. For example, normal reference values for the Mayo Clinic's SALCT test that determines cortisol level in saliva is <100 ng/dL; a saliva cortisol level higher than 100 ng/dL is thus an indication of hypercortisolemia. After being diagnosed with hypercortisolemia, the patient is subject to additional tests to confirm the presence of Cushing's syndrome.

c Cushing's Syndrome

At least one, preferably two or more, of the following tests are performed to diagnose Cushing's syndrome: 1) dexamethasone suppression test, which documents a loss of feedback inhibition of cortisol on the hypothalamic-pituitary-adrenal (HPA) axis; 2) 24-hour Urine Free Cortisol test, which assesses cortisol secretion in a 24-hour period; and 3) midnight salivary cortisol, which evaluates the loss of normal diurnal variation in cortisol secretion. If two of the three tests show abnormal cortisol levels, the Cushing's syndrome is confirmed.

The dexamethasone suppression test is typically used as a screen test for Cushing's syndrome. Dexamethasone is an exogenous steroid that binds glucocorticoid receptors in the anterior pituitary gland. When healthy individuals are treated with a low dose (1-2 mg) of dexamethasone, binding of dexamethasone to the glucocorticoid receptors provides negative feedback to the pituitary gland and results in suppression of ACTH secretion. The suppression of ACTH secretion, in turn, results in suppression of cortisol release and therefore a detectable decrease in cortisol level in circulation. In contrast, when patients having Cushing's syndrome are treated with a low dose of dexamethasone, no or little decrease in cortisol levels can be detected because of the excessive cortisol production associated with the disease. In one approach, the dexamethasone suppression test is performed by administering a low dose of dexamethasone, e.g., 1 mg, the night before at, e.g., 11 pm. The next morning, e.g., between 8-9 am; the patient's blood is then sampled and serum cortisol levels measured. Since normal subjects typically have serum cortisol levels reduced to less than 1.8 mg/dl, a serum cortisol level of more than 1.8 mg/dL is indicative of the presence of Cushing's syndrome,

The 24-hour Urine Free Cortisol test is the gold standard for diagnosing Cushing's syndrome. This test uses the principle that cortisol production is increased with Cushing's syndrome, and measurements of urinary excretion provide an integral estimate of that increase. A result more than the normal reference values is indicative of the presence of Cushing's syndrome. A 3 to 4-fold increase over normal reference values provides definite diagnosis of Cushing's syndrome; if this increase is present, no additional testing is required to confirm the diagnosis. For less dramatic increases in the urinary free-cortisol (UFC) level, other tests, such as the overnight dexamethasone suppression test and the midnight salivary cortisol test, as described above, are required.

The midnight saliva test is another test commonly used to confirm Cushing's syndrome. See the description of the test in the section above.

If the patient is confirmed to have Cushing's syndrome by two of the three tests, or by the detection of a 3 to 4-fold cortisol level increase in the 24-hour Urine Free Cortisol test, the next step is to measure ACTH to confirm he or she has ACTH-dependent Cushing's syndrome.

d ACTH-Dependent Cushing's Syndrome

There are two kinds of endogenous Cushing's syndrome: ACTH-dependent and ACTH-independent. The high cortisol level associated with ACTH-dependent Cushing's syndrome is caused by the overproduction of ACTH from a tumor, e.g., a pituitary tumor or an extrapituitary tumor. The excess cortisol level associated with ACTH-independent Cushing's syndrome, on the other hand, is caused by the overproduction of cortisol by a tumor in the adrenal gland or the overgrowth of the adrenal gland—either of which inhibits ACTH production and release. Thus, the ACTH levels are high in patients having ACTH-dependent Cushing's syndrome but low or even undetectable in patients having ACTH-independent Cushing's syndrome.

The biological samples that are suitable for ACTH determination can be serum, plasma, saliva, urine, or any other biological fluid taken from a subject. The sample can be the same or different from the sample used for cortisol level measurement. In some cases, the same sample that is used to measure cortisol level can be used to measure ACTH level. In other cases, different samples are used to measure cortisol and ACTH levels. For example, the cortisol levels can be measured in saliva and the ACTH levels can be measured in plasma. In yet other cases, different samples of the same type are used to measure the levels.

The level of ACTH can be measured using various methods, including but not limited to, immunoassays, e.g., competitive immunoassay, radioimmunoassay, immunofluorometric enzyme assay, and ELISA; competitive protein-binding assays; liquid chromatography (e.g., HPLC); and mass spectrometry, e.g., high-performance liquid chromatography/triple quadrupole-mass spectrometry (LC-MS/MS). Commercial kits for measuring ACTH are readily available, e.g., from Mayo clinic (Test ID: ACTH), Siemans Healthcare Global (Immulite® 2000 ACTH assay), and Roche Molecular Diagnostics (Catalog No. 03255751190).

A plasma ACTH concentration higher than the normal reference value indicates that the patient has ACTH-dependent Cushing's syndrome. Normal reference values vary depending on the assay method, type of sample, and timing of sample collection; like cortisol, ACTH in healthy individuals varies during a 24-hour period, reaching its highest level in the morning around 6-8 am and lowest at night around 11 pm. Various commercial kits provide the normal reference values in their testing protocols. For example, the normal reference values for Mayo Clinc Test ID: ACTH are about 10-60 pg/mL.

Patients diagnosed with ACTH-dependent Cushing's syndrome are selected, and the differential diagnosis performed as described below.

2. Method of Differential Diagnosis of ACTH-Dependent Cushing's Syndrome

The differential diagnosis method uses GRAs to discriminate between Cushing Disease and ectopic ACTH Cushing's syndrome, the two major forms of ACTH-dependent Cushing's syndrome. GRAs prevent cortisol from inhibiting both the CRH production in the hypothalamus and ACTH production in the pituitary gland through a negative feedback interaction, resulting in increased ACTH production and release. Patients with Cushing Disease have ACTH-producing tumors in the pituitary gland and thus will have a higher increase in ACTH level around the pituitary region than the

periphery region (outside the pituitary region). In contrast, patients with ectopic ACTH syndrome have the tumor growing outside the pituitary gland and thus will have a higher ACTH increase in the periphery than around the pituitary region. Thus a pituitary-to-periphery ratio can be used to discriminate between the two major types of ACTH-dependent Cushing's syndrome.

a Administration of GRA

GRA is administered at a dosage that is sufficient to increase ACTH in the pituitary gland by at least two fold in persons with normal HPA functions. In one embodiment, the GRA is mifepristone. In one embodiment, mifepristone is administered orally to the patient. In one embodiment, the mifepristone is administered at 300-1500 mg. In one embodiment, the GRA is administered at 11 pm the night before IPSS.

b. IPSS

The pituitary ACTH is measured from the blood sample obtained from the left, right, or both inferior petrosal sinuses (IPSs), which drain the pituitary gland. The periphery ACTH level is determined from the blood sample from a periphery vein. The procedure of sampling from inferior petrosal sinuses (known as IPSS) and the periphery is typically performed by an interventional radiologist.

IPSS is typically performed in the morning after administration of GRA, e.g., between 8 and 10 am, by advancing one or two microcatheters from the femoral vein up to one or both inferior petrosal sinuses. Meanwhile, another microcatheter is advanced to a periphery vein, e.g., the jugular vein. Venogram, or a digital venography, which documents the position of the catheters, is used to ensure the proper placement of the catheter; sampling begins only after confirming the microcatheter is positioned well in the IPS. Two samplings are made, at 5-10 minutes apart, by drawing blood simultaneously from the IPSs and the jugular vein at each sampling. Samples obtained are immediately placed in EDTA-containing tubes on ice. In some cases, an IPSS is performed only on one sinus, i.e., the left or right sinus. In some cases, the IPSS is performed for both sinuses (BIPSS). BIPSS provides values of ACTH from both right and left sinuses, a comparison of which provides useful information as to which side of the pituitary gland the tumor is located.

c. Diagnosis Based on the Central-to-Peripheral ACTH Ratio with Reference to Prolactin

The central-to-periphery ratio is the basis for the diagnosis; however the IPSS requires high level of expertise; since anomalous venous drainage, e.g., misplacement of the catherter tip when sampling the inferior petrosal sinus, may cause false negative results. In addition to IPSS venogram (described above), prolactin—which is also secreted by pituitary gland and circulated to the periphery—is often used as a marker for successful catheterization during IPSS. Prolactin levels are assessed from the same blood samples that are used for the ACTH analysis. A ratio of the central to periphery prolactin of more than 1.8 indicates successful catheterization.

Methods for measuring prolactin are known in the art. Useful assays include immunoassays, e.g., competitive immunoassay, radioimmunoassay, immunofluorometric enzyme assay, and ELISA; competitive protein-binding assay; and mass spectrometry, e.g., high-performance liquid chromatography/triple quadrupole-mass spectrometry (LC-MS/MS). Commerical kits for measuring prolactin are also readily available, e.g., from Abcam (Catalog # ab108655), R&D systems (Human Prolactin Quantikine ELISA Kit), and Cayman Chemical (Prolactin EIA Kit).

ACTH levels are determined using the methods described above. The patient's ACTH levels from one or both inferior petrosal sinuses are then compared with the ACTH levels in the periphery blood, and the petrosal sinus-to-periphery ACTH ratios are then determined. If the patient's inferior petrosal to periphery prolactin ratio is less than 1.8 (especially if less than 1.5)—an indication that the catheterization was improper—no diagnosis can be made and a new IPSS may need to be performed. If the patient's inferior petrosal-to-periphery prolactin ratio is more than 1.8 and the inferior petrosal-to-periphery ACTH ratio is greater than 3, he or she is then diagnosed as having Cushing Disease. If the patient's inferior petrosal-to-periphery prolactin ratio is more than 1.8 and the inferior petrosal-to periphery-ACTH ratio is less than 3, he or she is then diagnosed as having ectopic ACTH syndrome.

B. Establishing a Standard Control Level

As disclosed above, the differential diagnosis of ACTH dependent Cushing's syndrome involves comparisons of measurements of different hormones, e.g., prolactin, ACTH, and cortisol, with their respective normal reference values. In most cases, normal reference values, or standard control levels, are provided in the commercial kits that are used for the testing. Depending on circumstances, it may be necessary in some cases to establish a standard control level for the diagnosis. In order to establish a standard control for a particular sample type (e.g., a saliva sample, urine sample, plasma sample, or serum sample) for practicing the method of this disclosure, a group of healthy subjects, such as a group of subjects who do not have Cushing's Syndrome, is selected. These individuals are within the appropriate parameters, if applicable, for the purpose of diagnosing Cushing's Syndrome using the methods of the present invention. For instance, the individuals may be of similar age, gender, and comparable health status. Optionally, the individuals are of similar ethnic background.

The healthy status of the selected individuals can be confirmed by well-established, routinely employed methods, including but not limited to, general physical examination of the individuals and general review of their medical history.

Furthermore, the selected group of healthy individual must be of a reasonable size, such that the average amount, level, or concentration of cortisol, ACTH, or other steroid in the biological sample obtained from the group can be reasonably regarded as representative of the normal or average level among the general population of healthy individuals who do not experience Cushing's Syndrome. Preferably, the selected group comprises at least 10 normal, healthy human subjects.

Once an average value of cortisol, ACTH, or other steroid is established on the individual values found in each subject of the selected healthy control group, this average, median, or representative value or profile is considered a standard control level. A standard deviation is also determined during the same process. In some cases, separate standard control levels may be established for separately defined groups having distinct characteristics such as age, sex or ethnic background.

C. Glucocorticoid Receptor Antagonists

The methods of the present invention generally provide administering a GRA. In some cases, the glucocorticoid receptor antagonist is a specific GRA. As used herein, a specific glucocorticoid receptor antagonist refers to a composition or compound which inhibits any biological response associated with the binding of a glucocorticoid receptor to an agonist by preferentially binding to the glucocorticoid receptor rather than to another nuclear recep-

tor (NR). In some embodiments, the specific GRA binds preferentially to the glucocorticoid receptor rather than the mineralocorticoid receptor (MR), androgen receptor (AR), or progesterone receptor (PR). In an exemplary embodiment, the specific GRA binds preferentially to glucocorticoid receptor rather than the mineralocorticoid receptor (MR). In another exemplary embodiment, the specific GRA binds preferentially to the glucocorticoid receptor rather than the progesterone receptor (PR). In another exemplary embodiment, the specific GRA binds preferentially to the glucocorticoid receptor rather than the androgen receptor (AR). In yet another exemplary embodiment, the specific GRA binds preferentially to the glucocorticoid receptor in comparison to MR and PR, MR and AR, PR and AR, or MR, PR, and AR.

In a related embodiment, the specific GRA binds to the glucocorticoid receptor with an association constant ($K_d$) that is at least 10-fold less than the $K_d$ for other nuclear receptors. In another embodiment, the specific GRA binds to the glucocorticoid receptor with an association constant ($K_d$) that is at least 100-fold less than the $K_d$ for the other nuclear receptors. In another embodiment, the specific GRA binds to the glucocorticoid receptor with an association constant ($K_d$) that is at least 1000-fold less than the $K_d$ for the other nuclear receptors.

Generally, treatment can be provided by administering an effective amount of a GRA of any chemical structure or mechanism of action and a glucocorticosteroid of any chemical structure or mechanism of action. Provided herein, are classes of exemplary GRAs and specific members of such classes. However, one of skill in the art will readily recognize other related or unrelated GRAs that can be employed in the treatment methods described herein.

1. GRAs Having a Steroidal Backbone

In some embodiments, an effective amount of a GRA with a steroidal backbone is administered to a subject for treatment of an ACTH-secreting tumor. Steroidal GRAs can be obtained by modification of the basic structure of glucocorticoid agonists, i.e., varied forms of the steroid backbone. The structure of cortisol can be modified in a variety of ways. The two most commonly known classes of structural modifications of the cortisol steroid backbone to create GRAs include modifications of the 11-β hydroxy group and modification of the 17-β side chain (See, e.g., Lefebvre, J. Steroid Biochem. 33:557-563, 1989).

Examples of steroidal GR antagonists include androgen-type steroidal compounds as described in U.S. Pat. No. 5,929,058, and the compounds disclosed in U.S. Pat. Nos. 4,296,206; 4,386,085; 4,447,424; 4,477,445; 4,519,946; 4,540,686; 4,547,493; 4,634,695; 4,634,696; 4,753,932; 4,774,236; 4,808,710; 4,814,327; 4,829,060; 4,861,763; 4,912,097; 4,921,638; 4,943,566; 4,954,490; 4,978,657; 5,006,518; 5,043,332; 5,064,822; 5,073,548; 5,089,488; 5,089,635; 5,093,507; 5,095,010; 5,095,129; 5,132,299; 5,166,146; 5,166,199; 5,173,405; 5,276,023; 5,380,839; 5,348,729; 5,426,102; 5,439,913; 5,616,458, 5,696,127, and 6,303,591. Such steroidal GR antagonists include cortexolone, dexamethasone-oxetanone, 19-nordeoxycorticosterone, 19-norprogesterone, cortisol-21-mesylate; dexamethasone-21-mesylate, 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9-estradien-3-one (RU009), and (17α)-17-hydroxy-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one (RU044).

Other examples of steroidal antiglucocorticoids are disclosed in Van Kampen et al. (2002) Eur. J. Pharmacol. 457(2-3):207, WO 03/043640, EP 0 683 172 B1, and EP 0 763 541 B1, each of which is incorporated herein by reference. EP 0 763 541 B1 and Hoyberg et al., Int'l J. of Neuro-psychopharmacology, 5:Supp. 1, S148 (2002) disclose the compound (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one (ORG 34517), which in one embodiment, is administered in an amount effective to treat an ACTH-secreting tumor in a subject.

2. Removal or Substitution of the 11-β Hydroxy Group

Glucocorticoid antagonists with modified steroidal backbones comprising removal or substitution of the 11-β hydroxy group are administered in one embodiment of the invention. This class includes natural GRAs, including cortexolone, progesterone and testosterone derivatives, and synthetic compositions, such as mifepristone (Lefebvre, et al. supra). Preferred embodiments of the invention include all 11-β aryl steroid backbone derivatives because, in some cases, these compounds can be devoid of progesterone receptor (PR) binding activity (Agarwal, FEBS 217:221-226, 1987). In another embodiment an 11-β phenyl-aminodimethyl steroid backbone derivative, which is both an effective anti-glucocorticoid and anti-progesterone agent, is administered. These compositions can act as reversibly-binding steroid receptor antagonists. For example, when bound to a 11-β phenyl-aminodimethyl steroid, the steroid receptor can be maintained in a conformation that cannot bind its natural ligand, such as cortisol in the case of GR (Cadepond, 1997, supra).

Synthetic 11-beta phenyl-aminodimethyl steroids include mifepristone, also known as RU486, or 17-β-hydrox-11-β-(4-dimethyl-aminophenyl)17-α-(1-propynyl)estra-4,9-dien-3-one). Mifepristone has been shown to be a powerful antagonist of both the progesterone and glucocorticoid (GR) receptors. Thus, in some embodiments, the GRA administered to treat an ACTH-secreting tumor is mifepristone, or a salt, tautomer, or derivative thereof. In other embodiments, however, administration of mifepristone is specifically excluded as a GRA for treatment of an ACTH-secreting tumor.

Another 11-β phenyl-aminodimethyl steroid shown to have GR antagonist effects includes the dimethyl aminoethoxyphenyl derivative RU009 (RU39.009), 11-β-(4-dimethyl-aminoethoxyphenyl)-17-α-(propynyl-17-β-hydroxy-4,9-estradien-3-one) (see Bocquel, J. Steroid Biochem. Molec. Biol. 45:205-215, 1993). Another GR antagonist related to RU486 is RU044 (RU43.044) 17-β3-hydrox-17-α-19-(4-methyl-phenyl)-androsta-4,9(11)-dien-3-one) (Bocquel, 1993, supra). See also Teutsch, Steroids 38:651-665, 1981; U.S. Pat. Nos. 4,386,085 and 4,912,097.

One embodiment includes compositions that are irreversible anti-glucocorticoids. Such compounds include α-keto-methanesulfonate derivatives of cortisol, including cortisol-21-mesylate (4-pregnene-11-β, 17-α, 21-triol-3, 20-dione-21-methane-sulfonate and dexamethasone-21-mesylate (16-methyl-9-α-fluoro-1,4-pregnadiene-11β,17-α, 21-triol-3, 20-dione-21-methane-sulfonte). See Simons, J. Steroid Biochem. 24:25-32, 1986; Mercier, J. Steroid Biochem. 25:11-20, 1986; U.S. Pat. No. 4,296,206.

3. Modification of the 17-Beta Side Chain Group

Steroidal anti-glucocorticoids which can be obtained by various structural modifications of the 17-β side chain are also used in the methods of the invention. This class includes synthetic antiglucocorticoids, such as dexamethasone-oxetanone, various 17, 21-acetonide derivatives and 17-beta-carboxamide derivatives of dexamethasone (Lefebvre, 1989, supra; Rousseau, Nature 279:158-160, 1979).

4. Other Steroid Backbone Modifications

GRAs used in the various embodiments of the invention include any steroid backbone modification which effects a biological response resulting from a GR-agonist interaction. Steroid backbone antagonists can be any natural or synthetic variation of cortisol, such as adrenal steroids missing the C-19 methyl group, such as 19-nordeoxycorticosterone and 19-norprogesterone (Wynne, Endocrinology 107:1278-1280, 1980).

In general, the 11-β side chain substituent, and particularly the size of that substituent, can play a key role in determining the extent of a steroid's antiglucocorticoid activity. Substitutions in the A ring of the steroid backbone can also be important. For example, 17-hydroxypropenyl side chains can, in some cases, decrease antiglucocorticoid activity in comparison to 17-propynyl side chain containing compounds.

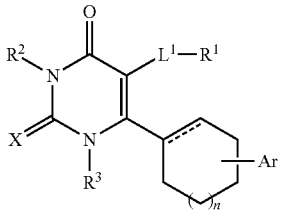
Additional glucocorticoid receptor antagonists known in the art and suitable for practice of the invention include 21-hydroxy-6,19-oxidoprogesterone (See Vicent, Mol. Pharm. 52:749-753, 1997), Org31710 (See Mizutani, J Steroid Biochem Mol Biol 42(7):695-704, 1992), RU43044, RU40555 (See Kim, J Steroid Biochem Mol Biol. 67(3): 213-22, 1998), and RU28362.

5. Non-Steroidal Anti-Glucocorticoids as Antagonists

Non-steroidal glucocorticoid receptor antagonists (GRAs) are also used in the methods of the invention to diagnose and treat Cushing's Syndrome in a subject. These include synthetic mimetics and analogs of proteins, including partially peptidic, pseudopeptidic and non-peptidic molecular entities. For example, oligomeric peptidomimetics useful in the invention include (α-β-unsaturated) peptidosulfonamides, N-substituted glycine derivatives, oligo carbamates, oligo urea peptidomimetics, hydrazinopeptides, oligosulfones and the like (See, e.g., Amour, Int. J. Pept. Protein Res. 43:297-304, 1994; de Bont, Bioorganic & Medicinal Chem. 4:667-672, 1996).

Examples of non-steroidal GR antagonists include the GR antagonist compounds disclosed in U.S. Pat. Nos. 5,696,127; 6,570,020; and 6,051,573; the GR antagonist compounds disclosed in US Patent Application 20020077356, the glucocorticoid receptor antagonists disclosed in Bradley et al., J. Med. Chem. 45, 2417-2424 (2002), e.g., 4α(S)-benzyl-2(R)-chloroethynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol ("CP 394531") and 4α(S)-benzyl-2(R)-prop-1-ynyl-1,2,3,4,4α,9,10,10α(R)-octahydro-phenanthrene-2,7-diol ("CP 409069"); and the compounds disclosed in PCT International Application No. WO 96/19458, which describes non-steroidal compounds that are high-affinity, highly selective antagonists for steroid receptors, such as 6-substituted-1,2-dihydro-N-protected-quinolines.

In some embodiments, Cushing's Syndrome is diagnosed and treated with an effective amount of a non-steroidal GRA having a cyclohexyl-pyrimidine backbone, a fused azadecalin backbone, a heteroaryl ketone fused azadecalin backbone, or an octahydro fused azadecalin backbone. For example, Cushing's Syndrome can be treated with effective amounts of one of the foregoing GRAs and a GC or a GC analog. Exemplary GRAs having a cyclohexyl-pyrimidine backbone include those described in U.S. Pat. No. 8,685,973. In some cases, the GRA having a cyclohexyl-pyrimidine backbone has the following structure:



wherein

the dashed line is absent or a bond;

X is selected from the group consisting of O and S;

$R^1$ is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, optionally substituted with from 1 to 3 $R^{1a}$ groups;

each $R^{1a}$ is independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl-$OR^{1b}$, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloaloxy, —$OR^{1b}$, —$NR^{1b}R^{1c}$, —$C(O)R^{1b}$, —$C(O)OR^{1b}$, —$OC(O)R^{1b}$, —$C(O)NR^{1b}R^{1c}$, —$NR^{1b}C(O)R^{1c}$, —$SO_2R^{1b}$, —$SO_2NR^{1b}R^{1c}$, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

$R^{1b}$ and $R^{1c}$ are each independently selected from the group consisting of H and $C_{1-6}$ alkyl;

$R^2$ is selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{1-6}$ alkyl-$OR^{1b}$, $C_{1-6}$ alkyl-$NR^{1b}R^{1c}$ and $C_{1-6}$ alkylene-heterocycloalkyl;

$R^3$ is selected from the group consisting of H and $C_{1-6}$ alkyl;

Ar is aryl, optionally substituted with 1-4 $R^4$ groups;

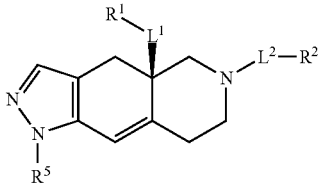
each $R^4$ is independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $C_{1-6}$ haloalkyl and $C_{1-6}$ haloalkoxy;

$L^1$ is a bond or $C_{1-6}$ alkylene; and

subscript n is an integer from 0 to 3,

or a salts and isomers thereof.

Exemplary GRAs having a fused azadecalin backbone include those described in U.S. Pat. Nos. 7,928,237; and 8,461,172. In some cases, the GRA having a fused azadecalin backbone has the following structure:



wherein

$L^1$ and $L^2$ are members independently selected from a bond and unsubstituted alkylene;

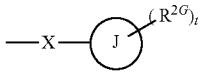
$R^1$ is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, —$OR^{1A}$, —$NR^{1C}R^{1D}$, —$C(O)NR^{1c}R^{1D}$, and —$C(O)OR^{1A}$, wherein

$R^{1A}$ is a member selected from hydrogen, unsubstituted alkyl and unsubstituted heteroalkyl,

$R^{1C}$ and $R^{1D}$ are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl,

wherein $R^{1C}$ and $R^{1D}$ are optionally joined to form an unsubstituted ring with the nitrogen to which they are attached, wherein said ring optionally comprises an additional ring nitrogen;

$R^2$ has the formula:



wherein

$R^{2G}$ is a member selected from hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, —CN, and —$CF_3$;

J is phenyl;

t is an integer from 0 to 5;

X is —$S(O_2)$—; and

$R^5$ is phenyl optionally substituted with 1-5 $R^{5A}$ groups, wherein

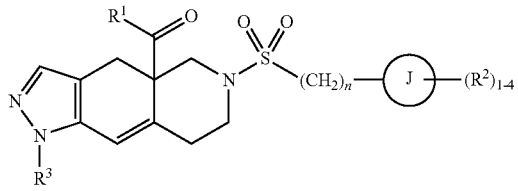
$R^{5A}$ is a member selected from hydrogen, halogen, —$OR^{5A1}$, —$S(O_2)NR^{5A2}R^{5A3}$, —CN, and unsubstituted alkyl, wherein

$R^{5A1}$ is a member selected from hydrogen and unsubstituted alkyl, and

$R^{5A2}$ and $R^{5A3}$ are members independently selected from hydrogen and unsubstituted alkyl,

or salts and isomers thereof.

Exemplary GRAs having a heteroaryl ketone fused azadecalin backbone include those described in U.S. 2014/0038926. In some cases, the GRA having a heteroaryl ketone fused azadecalin backbone has the following structure:



wherein

$R^1$ is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from $R^{1a}$;

each $R^{1a}$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, —CN, N-oxide, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl;

ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each $R^2$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, $C_{1-6}$ alkyl-$C_{1-6}$ alkoxy, —CN, —OH, —$NR^{2a}R^{2b}$, —$C(O)R^{2a}$, —$C(O)OR^{2a}$, —$C(O)NR^{2a}R^{2b}$, —$SR^{2a}$, —$S(O)R^{2a}$, —$S(O)_2R^{2a}$, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 $R^{2c}$ groups;

alternatively, two $R^2$ groups linked to the same carbon are combined to form an oxo group (=O);

alternatively, two $R^2$ groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 $R^{2d}$ groups;

$R^{2a}$ and $R^{2b}$ are each independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl;

each $R^{2c}$ is independently selected from the group consisting of hydrogen, halogen, hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, —CN, and —$NR^{2a}R^{2b}$;

each $R^{2d}$ is independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl, or two $R^{2d}$ groups attached to the same ring atom are combined to form (=O);

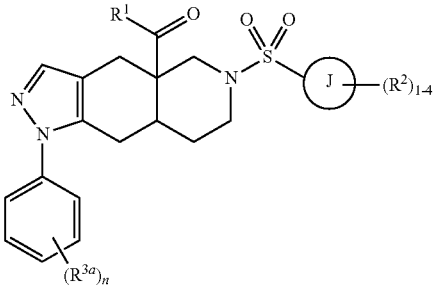
$R^3$ is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 $R^{3a}$ groups;

each $R^{3a}$ is independently selected from the group consisting of hydrogen, halogen, and $C_{1-6}$ haloalkyl; and

subscript n is an integer from 0 to 3;

or salts and isomers thereof.

Exemplary GRAs having an octohydro fused azadecalin backbone include those described in U.S. Provisional Patent Appl. No. 61/908,333, entitled Octahydro Fused Azadecalin Glucocorticoid Receptor Modulators, filed on Nov. 25, 2013. In some cases, the GRA having an octohydro fused azadecalin backbone has the following structure:



wherein

$R^1$ is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from $R^{1a}$;

each $R^{1a}$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, N-oxide, and $C_{3-8}$ cycloalkyl;

ring J is selected from the group consisting of an aryl ring and a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each $R^2$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, $C_{1-6}$ alkyl-$C_{1-6}$ alkoxy, —CN, —OH, —$NR^{2a}R^{2b}$, —$C(O)R^{2a}$, —$C(O)OR^{2a}$, —$C(O)NR^{2a}R^{2b}$, —$SR^{2a}$, —$S(O)R^{2a}$, —$S(O)_2R^{2a}$, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl having from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S;

alternatively, two $R^2$ groups on adjacent ring atoms are combined to form a heterocycloalkyl ring having from

5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 $R^{2c}$ groups;

$R^{2a}$, $R^{2b}$ and $R^{2c}$ are each independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl;

each $R^{3a}$ is independently halogen; and

subscript n is an integer from 0 to 3;

or salts and isomers thereof.

D. Pharmaceutical Compositions of Glucocorticoid Receptor Antagonists

The GRA compositions of the present disclosure can be prepared in a wide variety of oral, parenteral and topical dosage forms. Oral preparations of either include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. The GRA compositions of the present invention can also be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the GRA compositions described herein can be administered by inhalation, for example, intranasally. Additionally, the GRA compositions of the present invention can be administered transdermally. The GRA compositions of this invention can also be administered by intraocular, intravaginal, and intrarectal routes including suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, J. Clin. Pharmacol. 35:1187-1193, 1995; Tjwa, Ann. Allergy Asthma Immunol. 75:107-111, 1995). Accordingly, the present invention provides pharmaceutical compositions of a GRA including a pharmaceutically-acceptable carrier or excipient and a GRA compound of the present invention.

For preparing pharmaceutical compositions from the GRA compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co, Easton Pa. ("Remington's").

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5% or 10% to 70% of the compounds of the present invention.

Suitable solid excipients include, but are not limited to, magnesium carbonate; magnesium stearate; talc; pectin; dextrin; starch; tragacanth; a low melting wax; cocoa butter; carbohydrates; sugars including, but not limited to, lactose, sucrose, mannitol, or sorbitol, starch from corn, wheat, rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins including, but not limited to, gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound (i.e., dosage). Pharmaceutical preparations of the invention can also be used orally using, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain the compounds of the present invention mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the compounds of the present invention may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the compounds of the present invention are dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving one or more compounds of the present invention in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

Oil suspensions can be formulated by suspending the compounds of the present invention in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as

glycerol, sorbitol or sucrose. These formulations can be preserved by the addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, J. Pharmacol. Exp. Ther. 281:93-102, 1997. The pharmaceutical formulations of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

The GRA compositions provided herein can also be delivered as microspheres for slow release in the body. For example, microspheres can be formulated for administration via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, J. Biomater Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao Pharm. Res. 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. Pharm. Pharmacol. 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months.

In another embodiment, the GRA compositions of the present invention can be formulated for parenteral administration, such as intravenous (IV) administration or administration into a body cavity or lumen of an organ. The formulations for administration will commonly comprise a solution of the compositions of the present invention dissolved in a pharmaceutically acceptable carrier. Among the acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. These GRA formulations may be sterilized by conventional, well known sterilization techniques. The formulations may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents, e.g., sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of the compositions of the present invention in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. For IV administration, the GRA formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol.

In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, e.g., Al-Muhammed, J. *Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989).

Lipid-based drug delivery systems include lipid solutions, lipid emulsions, lipid dispersions, self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS). In particular, SEDDS and SMEDDS are isotropic mixtures of lipids, surfactants and co-surfactants that can disperse spontaneously in aqueous media and form fine emulsions (SEDDS) or microemulsions (SMEDDS). Lipids useful in the formulations of the present invention include any natural or synthetic lipids including, but not limited to, sesame seed oil, olive oil, castor oil, peanut oil, fatty acid esters, glycerol esters, Labrafil®, Labrasol®, Cremophor®, Solutol®, Tween®, Capryol®, Capmul®, Captex®, and Peceol®.

The GRA composition can also contain other compatible therapeutic agents. The compounds described herein can be used in combination with one another, with other active agents known to be useful in antagonizing a glucocorticoid receptor, or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

E. Administration

The GRA compounds or compositions of the present invention can be delivered by any suitable means, including oral, parenteral (e.g., intravenous injection or intramuscular injection) and topical methods. Transdermal administration methods, by a topical route, can be formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the compounds and compositions of the present invention. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

GRAs can be administered orally. For example, the GRA can be administered as a pill, a capsule, or liquid formulation as described herein. Alternatively, GRAs can be provided via parenteral administration. For example, the GRA can be administered intravenously (e.g., by injection or infusion). Additional methods of administration of the compounds described herein, and pharmaceutical compositions or formulations thereof, are described herein.

In some embodiments, the GRA is administered in one dose. In other embodiments, the GRA is administered in more than one dose, e.g., 2 doses, 3 doses, 4 doses, 5 doses, 6 doses, 7 doses, or more. In some cases, the doses are of an equivalent amount. In other cases, the doses are of different amounts. The doses can increase or taper over the duration of administration. The amount will vary according to, for example, the GRA properties. To determine an effective dose, the GRA must elevate the level of ACTH by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function.

In some embodiments, the subject diagnosed as having Cushing's Syndrome is administered a therapeutically effective amount of a GRA to ameliorate at least one symptom of Cushing's Syndrome. In some case, therapeutically effective amount of the GRA can be administered to treat Cushing's Syndrome.

## IV. Examples

### Example 1 Diagnosis of Hypercortisolemia

A 45-year-old female visits her endocrinologist. She appears to have abdominal obesity, thin arms and legs, a round red face, and a fat lump between the shoulders. She has acne and reddish purple stretch marks in the body that are more than 1 cm wide. She describes having fragile skin that heals poorly, irregular menstruation, and she often feels changes in mood, headaches, and a chronic feeling of tiredness. Her physical examination records show that she has proximal muscle weakness and osteoporosis. Her blood tests indicate that she has low potassium, diabetes and elevated blood pressure. She has not been taken exogenous glucocorticoid drugs prior to this visit. Her endocrinologist suspects she has hypercortisolemia, and orders a late night saliva cortisol test for her.

She complies to the requirement not to brush, eat, or drink for 30 minutes prior to the saliva collection. At midnight she collected her saliva by placing a swab into her mouth, while rolling the swab, for approximately 2 minutes. The sample is assayed using Mayo Clinic Test ID: SALCT following the protocol provided with the test. The result shows that her cortisol level is 200 ng/dL, indicating that she has hypercortisolemia.

### Example 2. Diagnosis of Cushing's Syndrome

After diagnosis of hypercortisolemia, additional tests are ordered for her to determine whether she has Cushing's syndrome. First, a dexamethasone suppression test is performed. She is given 1 mg of dexamethasone at 11 pm, and the next morning her blood sample are collected between 8-9 am. Serum are collected from the blood and measured for cortisol using Mayo Clinic Test ID: CORT (http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8545), according to manufacturer's instructions. Her serum cortisol level is 2.2 mcg/dl, consistent with the presence of Cushing's syndrome.

Next, a 24 hour urine collection is ordered to measure her urine free cortisol. 3 mL of her 24-hour urine specimen is collected into a container, with the addition of 10 gram of boric acid as a preservative. The sample is centrifuged and removed of precipitate before the assay. Cortisol content is analyzed using Mayo Clinic Test ID: COCOU, according to manufacturer's instructions (http://www.mayomedicallaboratories.com/test-catalog/Specimen/82948). The test shows a cortisol level of 180 mcg—4 fold of the upper limit of the normal range of cortisol for the test: 3.5-45 mcg. Based on her 24-hour urine excretion test result as well as her clinical symptoms, she is diagnosed as having Cushing's syndrome. The next step is to measure ACTH to differentiate between ACTH-dependent and ACTH-independent Cushing's syndrome.

### Example 3. Diagnosis of ACTH-Dependent Cushing's Syndrome

A blood test is then performed to determine her plasma ACTH level. 1 mL of whole blood sample is drawn from her in the morning. The blood is spun down in a refrigerated centrifuge and the plasma is immediately separated from cells. 0.5 mL of the plasma sample is assayed for ACTH using Mayo Clinic Test ID: ACTH, following the manufacturer's instructions (http://www.mayomedicallaboratories.com/test-catalog/Specimen/8411). The result shows her plasma ACTH is 80 pg/mL, which indicates that she has ACTH-dependent Cushing's syndrome.

### Example 4. Diagnosis of Cushing Disease

Following the diagnosis of ACTH dependent Cushing's syndrome, she then undergoes IPSS to identify the source of abnormal ACTH secretion, i.e., whether it is pituitary or ectopic. Mifepristone administration and IPSS are performed to determine the cause of her ACTH-dependent Cushing's syndrome. She first takes an oral dose of 300-1500 mg of mifepristone at 11 pm the night before IPSS. Mifepristone at this dose is sufficient to increase ACTH from the pituitary gland by at least two-fold in persons having normal hypothalamic-pituitary-adrenal axis (HPA) function. Between 8 to 10 am, an interventional radiologist performs a femoral microcatheterization, in which two 0.018 inch microcatheters are advanced from the femoral vein up to her right and left inferior petrosal sinuses (IPS). Another 0.018 microcatherter is inserted into the peripheral jugular vein. A 5,000 unit bolus of heparin is administered to the veins to prevent venous sinus thrombosis.

After the microcathers enter the sinuses and the jugular bulb, a diagnostic venography is performed, in which a rapid injection of contrast is performed to attempt to reflux contrast into the inferior petrosal sinus to guide placement of a microcatheter. After confirming the position of the microcatheter and positioning it well in the IPS, two samplings are made at 5-10 minutes apart. Blood samples are drawn simultaneously from the IPS and the jugular vein at each sampling and immediately placed in EDTA-containing tubes on ice.

One half of each blood sample is centrifuged for 10 minutes at 1,000-2,000 g to remove the cells and collect plasma. The other half is left undisturbed at room temperature for 30 minutes to clot, and serum is obtained after removal of the clot by a centrifugation. The plasma samples from both the jugular vein and the IPS are assayed for ACTH using Mayo Clinic's Test ID: ACTH, as described above. The serum samples are assayed for prolactin using Mayo Clinic's Test ID: PLPMA, following the manufacturer's instructions. The results show that the prolactin level in her left IPS is 25 ng/ml and right IPS is 24 ng/ml. The prolactin level in her jugular vein is 12 ng/ml. The ACTH level in her IPS is 800 pg/ml and the ACTH in her jugular vein is 200 pg/ml.

Her IPSs (both left and right) to jugular vein prolactin ratio is greater than 1.8, which reflects the correct central-to-periphery gradient, thus confirming the correct positioning of the catheterization. Her IPSs to jugular vein ACTH ratio is greater than 3, which indicates she has Cushing Disease.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference.

What is claimed is:

**1**. A method of concurrently treating Cushing's syndrome and differentially diagnosing adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient where the differential diagnosis is between ectopic ACTH syndrome and Cushing's disease, the method comprising the steps of:

(i) selecting a patient with Cushing's syndrome and also elevated ACTH levels;

(ii) administering a dose of glucocorticoid receptor antagonist (GRA) sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function;

(iii) waiting for at least two hours; and,

(iv) obtaining from the patient an ACTH concentration ratio wherein the ratio is derived from the ACTH concentrations in fluid obtained from either the left or right inferior petrosal venous sinus and from fluid obtained from a periphery venous sample;

wherein an ACTH concentration ratio of greater than 3 for the ACTH concentration from the inferior venous sinus sample over the periphery venous sinus sample is diagnostic of Cushing's disease.

**2**. The method of claim **1** wherein the periphery venous sample is a jugular venous sample.

**3**. The method of claim **1** wherein the glucocorticoid receptor antagonist is a selective inhibitor of the glucocorticoid receptor.

**4**. The method of claim **1** wherein a first and second sampling of the ACTH concentrations in the are taken 5-10 minutes apart from both the inferior petrosal venous sinus and a periphery venous sample.

**5**. The method of claim **1**, wherein the glucocorticoid receptor antagonist comprises a steroidal backbone with at least one phenyl-containing moiety in the 11-β position of the steroidal backbone.

**6**. The method of claim **5** wherein the phenyl-containing moiety in the 11-β position of the steroidal backbone is a dimethylaminophenyl moiety.

**7**. The method of claim **5**, wherein the glucoocoricoid receptor antagonist is mifepristone.

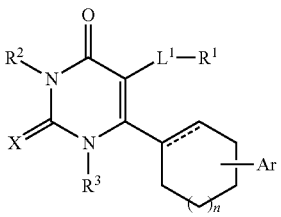
**8**. The method of claim **1**, wherein the glucocorticoid receptor antagonist is selected from the group consisting of 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9 estradien-3-one and (17α)-17-hydroxy-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one.

**9**. The method of claim **1**, wherein the glucocorticoid receptor antagonist is (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one.

**10**. The method of claim **1**, wherein the glucocorticoid receptor antagonist has a non-steroidal backbone.

**11**. The method of claim **10**, wherein the glucocorticoid receptor antagonist backbone is a cyclohexyl pyrimidine.

**12**. The method of claim **11**, wherein the cyclohexyl pyrimidine has the following formula:



wherein

the dashed line is absent or a bond;

X is selected from the group consisting of O and S;

$R^1$ is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, optionally substituted with from 1 to 3 $R^{1a}$ groups;

each $R^{1a}$ is independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl $OR^{1b}$, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ haloaloxy, $OR^{1b}$, $NR^{1b}R^{1c}$, $C(O)R^{1b}$, $C(O)OR^{1b}$, $OC(O)R^{1b}$, $C(O)NR^{1b}R^{1c}$, $NR^{1b}C(O)R^{1c}$, $SO_2R^{1b}$, $SO_2NR^{1b}R^{1c}$, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

$R^{1b}$ and $R^{1c}$ are each independently selected from the group consisting of H and $C_{1-6}$ alkyl;

$R^2$ is selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{1-6}$ alkyl-$OR^{1b}$, $C_{1-6}$ alkyl $NR^{1b}R^{1c}$ and $C_{1-6}$ alkylene heterocycloalkyl;

$R^3$ is selected from the group consisting of H and $C_{1-6}$ alkyl;

Ar is aryl, optionally substituted with 1-4 $R^4$ groups;

each $R^4$ is independently selected from the group consisting of H, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, halogen, $C_{1-6}$ haloalkyl and $C_{1-6}$ haloalkoxy;

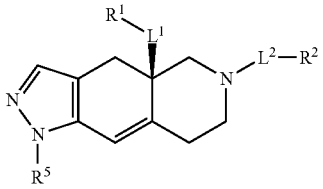
$L^1$ is a bond or $C_{1-6}$ alkylene; and

subscript n is an integer from 0 to 3,

or salts thereof.

**13**. The method of claim **10**, wherein the glucocorticoid receptor antagonist backbone is a fused azadecalin.

**14**. The method of claim **13**, wherein the fused azadecalin is a compound having the following formula:



wherein

$L^1$ and $L^2$ are members independently selected from a bond and unsubstituted alkylene;

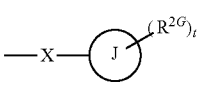
$R^1$ is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, —$OR^{1A}$, $NR^{1C}R^{1D}$, —$C(O)NR^{1C}R^{1D}$, and —$C(O)OR^{1A}$, wherein

$R^{1A}$ is a member selected from hydrogen, unsubstituted alkyl and unsubstituted heteroalkyl,

$R^{1C}$ and $R^{1D}$ are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl,

wherein $R^{1C}$ and $R^{1D}$ are optionally joined to form an unsubstituted ring with the nitrogen to which they are attached, wherein said ring optionally comprises an additional ring nitrogen;

$R^2$ has the formula:



wherein

$R^{2G}$ is a member selected from hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl,

unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, —CN, and —$CF_3$;

J is phenyl;

t is an integer from 0 to 5;

X is —$S(O_2)$—; and

$R^5$ is phenyl optionally substituted with 1-5 $R^{5A}$ groups, wherein

$R^{5A}$ is a member selected from hydrogen, halogen, —$OR^{5A1}$, $S(O_2)NR^{5A2}R^{5A3}$, —CN, and unsubstituted alkyl, wherein

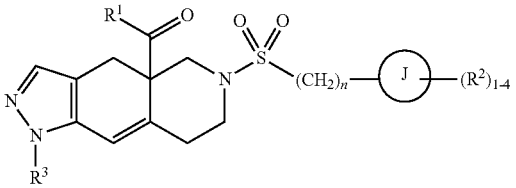
$R^{5A1}$ is a member selected from hydrogen and unsubstituted alkyl, and

$R^{5A2}$ and $R^{5A3}$ are members independently selected from hydrogen and unsubstituted alkyl,

or salts thereof.

**15**. The method of claim **10**, wherein the glucocorticoid receptor antagonist backbone is a heteroaryl ketone fused azadecalin or an octahydro fused azadecalin.

**16**. The method of claim **15**, wherein the heteroaryl ketone fused azadecalin has the formula:



wherein

$R^1$ is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from $R^{1a}$;

each $R^{1a}$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, CN, N-oxide, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl;

ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each $R^2$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, $C_{1-6}$ alkyl-$C_{1-6}$ alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, $SR^{2a}$, $S(O)R^{2a}$, $S(O)_2R^{2a}$, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 $R^{2c}$ groups;

alternatively, two $R^2$ groups linked to the same carbon are combined to form an oxo group (=O);

alternatively, two $R^2$ groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 $R^{2d}$ groups;

$R^{2a}$ and $R^{2b}$ are each independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl;

each $R^{2c}$ is independently selected from the group consisting of hydrogen, halogen, hydroxy, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, CN, and $NR^{2a}R^{2b}$;

each $R^{2d}$ is independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl, or two $R^{2d}$ groups attached to the same ring atom are combined to form (=O);

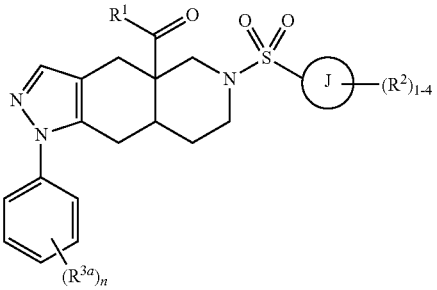
$R^3$ is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 $R^{3a}$ groups;

each $R^{3a}$ is independently selected from the group consisting of hydrogen, halogen, and $C_{1-6}$ haloalkyl; and

subscript n is an integer from 0 to 3;

or salts thereof.

**17**. The method of claim **15**, wherein the octahydro fused azadecalin has the formula:



wherein

$R^1$ is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from $R^{1a}$;

each $R^{1a}$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, N-oxide, and $C_{3-8}$ cycloalkyl;

ring J is selected from the group consisting of an aryl ring and a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each $R^2$ is independently selected from the group consisting of hydrogen, $C_{1-6}$ alkyl, halogen, $C_{1-6}$ haloalkyl, $C_{1-6}$ alkoxy, $C_{1-6}$ haloalkoxy, $C_{1-6}$ alkyl-$C_{1-6}$ alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, $SR^{2a}$, $S(O)R^{2a}$, $S(O)_2R^{2a}$, $C_{3-8}$ cycloalkyl, and $C_{3-8}$ heterocycloalkyl having from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S;

alternatively, two $R^2$ groups on adjacent ring atoms are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 $R^{2c}$ groups;

$R^{2a}$, $R^{2b}$ and $R^{2c}$ are each independently selected from the group consisting of hydrogen and $C_{1-6}$ alkyl;

each $R^{3a}$ is independently halogen; and

subscript n is an integer from 0 to 3,

or salts thereof.

**18**. A method of concurrently treating Cushing's syndrome and obtaining a measurement indicative of differen-

tial diagnosis of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient where the differential diagnosis is between ectopic ACTH syndrome and Cushing's disease, the method comprising the steps of:

determining the ACTH concentration ratio from a patient with Cushing's syndrome and an elevated ACTH level,

where the patient has been administered a dose of glucocorticoid receptor antagonist (GRA) at least two hours prior to the removal of venous samples and

where the amount of GRA administered to the patient is sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function;

wherein the ACTH concentration ratio is derived from the ACTH concentrations in fluid obtained from either the left or right inferior petrosal venous sinus and from fluid obtained from a periphery venous sample; and

wherein an ACTH concentration ratio of greater than 3 for the ACTH concentration from the inferior venous sinus sample over the periphery venous sinus sample is indicative of Cushing's disease.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION



PATENT NO. : 9,829,495 B2
APPLICATION NO. : 15/236015
DATED : November 28, 2017
INVENTOR(S) : Andreas G. Moraitis

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

In Column 33, Claim 4, Line 30, remove "in the";

In Column 33, Claim 7, Line 40, remove "glucoocoricoid" and insert --glucocorticoid--;

In Column 35, Claim 16, Line 50, remove "halogen, $C_{1\ 6}$" and insert --halogen, $C_{1-6}$--; and,

In Column 35, Claim 16, Line 51, remove "$C_{1\ 6}$ alkoxy" and insert --$C_{1-6}$ alkoxy--.

Signed and Sealed this
Twenty-sixth Day of December, 2017

Joseph Matal

Joseph Matal
*Performing the Functions and Duties of the*
*Under Secretary of Commerce for Intellectual Property and*
*Director of the United States Patent and Trademark Office*

# EXHIBIT D

US010500216B2

(12) **United States Patent**
**Belanoff et al.**

(10) **Patent No.: US 10,500,216 B2**
(45) **Date of Patent: Dec. 10, 2019**

(54) **OPTIMIZING MIFEPRISTONE ABSORPTION**

(71) Applicant: **CORCEPT THERAPEUTICS, INC.**, Menlo Park, CA (US)

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(73) Assignee: **Corcept Therapeutics, Inc.**, Menlo Park, CA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 110 days.

(21) Appl. No.: **13/677,465**

(22) Filed: **Nov. 15, 2012**

(65) **Prior Publication Data**

US 2013/0131030 A1 May 23, 2013

**Related U.S. Application Data**

(60) Provisional application No. 61/561,644, filed on Nov. 18, 2011.

(51) **Int. Cl.**
***A61K 31/575*** (2006.01)
***A61K 31/567*** (2006.01)

(52) **U.S. Cl.**
CPC ..... ***A61K 31/575*** (2013.01); ***A61K 31/567*** (2013.01)

(58) **Field of Classification Search**
CPC ..... A61K 31/567; A61K 31/575
USPC ..... 514/179
See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides a method for altering the pharmacokinetics of mifepristone upon oral administration. Mifepristone absorption into the blood is increased upon administration with meals. The method of the invention can benefit patients suffering from conditions including psychiatric illnesses and hormonal disorders.

**4 Claims, No Drawings**

# OPTIMIZING MIFEPRISTONE ABSORPTION

## CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 61/561,644, filed Nov. 18, 2011, which is incorporated in its entirety herein for all purposes.

## BACKGROUND OF THE INVENTION

The term "food effect" refers to a somewhat unpredictable phenomenon that can influence the absorption of drugs from the gastrointestinal tract following oral administration. A food effect can be designated negative when absorption is decreased, or positive when absorption is increased and manifested as an increase in oral bioavailability (as reflected by total exposure). Alternatively, food effects can refer to changes in maximum concentration, or the time to reach maximum concentration, independently of overall absorption. As a result, some drugs have to be taken in either fasted or fed conditions to achieve the optimum effect. For example, patients may be instructed to take a drug with a meal, before a meal (e.g., one hour before a meal), or after a meal (e.g., two hours after a meal). However, many drugs are unaffected by food, and thus, can be taken in either a fasted or a fed condition.

Mifepristone is a synthetic steroid that binds progesterone and glucocorticoid receptors and has been employed to treat a number of conditions including meningioma, uterine fibroids, hyperadrenocorticism, and certain psychiatric illnesses. It has been surprisingly discovered that administration of the same dose of mifepristone can produce widely varying plasma drug concentration in different patients. For the same dose of mifepristone, the plasma drug concentration can differ by as much as 800% from one patient to another. The varied plasma drug concentration can result in some patients not receiving an efficacious dose of mifepristone. For these patients in particular, it is necessary to improve the pharmacokinetics of mifepristone upon administration. Surprisingly, the present invention meets this and other needs.

## BRIEF SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a method for increasing mifepristone absorption in a patient suffering from a disorder or condition amenable to treatment by mifepristone. The method includes administering a dosage of from about 100 to about 2000 mg mifepristone to the patient within 1 hour of consuming a meal, such that the pharmacokinetics of mifepristone are altered by increasing the maximum plasma concentration ($C_{max}$) and increasing the area under the curve (AUC) compared to administering mifepristone without food, thereby increasing mifepristone absorption in the patient.

In a second embodiment, the invention provides a method for improving absorption of mifepristone in a patient suffering from psychotic major depression. The method includes administering a dose of from about 100 mg to about 2000 mg mifepristone to the patient within 1 hour after consuming a meal, such that the pharmacokinetics of mifepristone are altered by increasing the maximum plasma concentration ($C_{max}$) and increasing the area under the curve (AUC) compared to administering mifepristone without food, thereby increasing mifepristone absorption.



In a third embodiment, the invention provides a method of improving absorption of mifepristone in a patient suffering from Cushing's Syndrome. The method includes administering a dose of from about 100 mg to about 2000 mg mifepristone to the patient within 1 hour after consuming a meal, such that the pharmacokinetics of mifepristone are altered by increasing the maximum plasma concentration ($C_{max}$) and increasing the area under the curve (AUC) compared to administering mifepristone without food, thereby increasing mifepristone absorption.

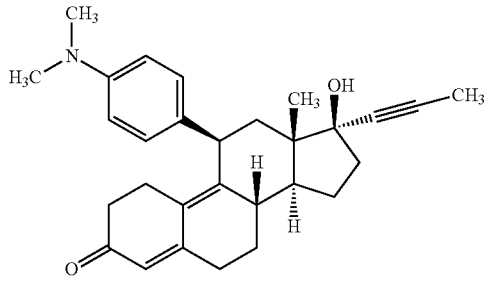
## DETAILED DESCRIPTION OF THE INVENTION

### I. General

The present invention provides a method for altering the pharmacokinetics of mifepristone upon oral administration. Mifepristone absorption into the blood of a patient is increased upon administration following a meal, serving to enhance the therapeutic benefit of a given dose as well as prevent adverse effects associated with higher dosages. The methods of the invention can be of special benefit to patients suffering from psychiatric illnesses and endocrine disorders.

### II. Definitions

The term "mifepristone" refers to a compound having the following structure:




The term mifepristone also refers to a family of compositions also known as: RU486 or RU38.486; 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one); 11-beta-(4dimethylaminophenyl)-17-beta-hydroxy-17-alpha-(1-propynyl)-estra-4,9-dien-3-one); 11B-[p-(Dimethylamino) phenyl]-17B-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one; 11B-(4-dimethyl-aminophenyl)-17B-hydroxy-17A-(prop-1-ynyl)-estra-4,9-dien-3-one; 17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A-(propynyl-1)-estra-4,9-diene-3-one; 17B-hydroxy-11B-(4-dimethylaminophenyl-1)-17A-(propynyl-1)-E; (11B,17B)-11-[4-dimethylamino)-phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one; and 11B-[4-(N,N-dimethylamino)phenyl]-17A-(prop-1-ynyl)-D-4,9-estradiene-17B-ol-3-one. Salts, hydrates and prodrug forms of mifepristone are also useful in the formulations of the present invention.

Mifepristone and its analogs bind to the glucocorticoid receptor (GR), typically with high affinity, and inhibit the biological effects initiated/mediated by the binding of any cortisol or cortisol analogue to the GR. As such, mifepristone has been used to treat conditions associated with elevated cortisol levels including, for example, hyperadrenocorticism, also known as Cushing's syndrome (Chrousos,

pp 273-284, In: Baulieu, ed. *The Antiprogestin Steroid RU 486 and Human Fertility Control*. Plenum Press, New York (1989), Sartor (1996) *Clin. Obstetrics and Gynecol.* 39:506-510). Patients with some forms of psychiatric illnesses can be responsive to treatments which block the effect of cortisol, as by administering GR antagonists (Van Look (1995) *Human Reproduction Update* 1:19-34). In one study, a patient with depression associated with Cushing's Syndrome was responsive to a high dose, up to 1400 mg per day, of mifepristone (Nieman (1985) *J. Clin Endocrinol. Metab.* 61:536). Due to its antiprogestogenic activity, mifepristone has also been employed in emergency contraception, medical abortion, and treatment of uterine fibroids and meningioma (Healy (2009) *Australian Prescriber* 32:152-154).

The term "increasing mifepristone absorption" refers to promoting the entrance of mifepristone into blood upon administration to the subject. "Improving mifepristone absorption" refers to increasing the level of mifepristone in the bloodstream of a subject treated via the method of the invention.

The term "meal" refers to a meal as defined by the FDA food effect test guidelines and can include a high-fat, low-fat or other type of meal. A high-fat meal is one where approximately 50 percent of total caloric content of the meal is fat. Also included are high-calorie meals having approximately 800 to 1000 calories. The meal can have approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. An example test meal includes two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Another example of a meal includes a moderate fat breakfast (34% of total calories from fat), which on average contains 27 g protein (13%), 32 g fat (34%), and 111 g carbohydrate (53%), totaling approximately 836 calories.

The term "$C_{max}$" refers to the maximum observed plasma concentration of mifepristone resulting from administration via a method of the present invention or via an alternative route.

The term "area under the curve" (AUC) refers to the integral of a plot of mifepristone concentration in plasma vs. time during or after administration.

The term "patient" refers to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. The patient can have a condition known to be treated by glucocorticoid antagonists such as mifepristone. Such conditions include, but are not limited to, psychiatric illnesses and hormonal disorders. In certain embodiments, the patient is a human. The patient can be male or female.

The term "administering mifepristone without food" refers to administering mifepristone more than one hour after food has been ingested by the patient to whom it is administered. "Administration of mifepristone in the absence of the meal" refers to mifepristone administration without prior consumption of a meal by a patient under the same conditions as those after which increased mifepristone absorption is observed. The conditions include, but are not limited to, the nutritional content of the meal and the timing with respect to mifepristone administration.

The term "oral dosage form" refers to a formulation or preparation of a therapeutic agent suitable for ingestion by a subject via mouth. Preferably, the therapeutic agent is mifepristone. Oral dosage forms can include but are not limited to liquid solutions, suspensions, emulsions, tablets, capsules, and lozenges.

The term "unit dosage form" refers to physically discrete units, such as capsules or tablets suitable as unitary dosages for human patients and other subjects, each unit containing a predetermined quantity of a therapeutic agent calculated to produce the desired therapeutic effect. Preferably, the therapeutic agent is mifepristone. Unit dosage form can include additional therapeutic agents as well as pharmaceutically acceptable carriers, diluents, excipients, or combinations thereof.

## III. Method for Increasing Mifepristone Absorption

The present invention provides a method for increasing mifepristone absorption in a patient suffering from a disorder or condition amenable to treatment by a glucocorticoid receptor antagonist (GRA) using any suitable dosage of mifepristone by administering the mifepristone following consumption of food by the patient. In some embodiments, the present invention provides a method for increasing mifepristone absorption in a patient suffering from a disorder or condition amenable to treatment by mifepristone, including administering to the patient a dosage of from about 100 to about 2000 mg mifepristone within 1 hour of consuming a meal, such that the pharmacokinetics of mifepristone are altered by increasing the maximum plasma concentration ($C_{max}$) and increasing the area under the curve (AUC) compared to administering mifepristone without food, thereby increasing mifepristone absorption in the patient.

### A. Formulations and Administration

Mifepristone can be administered at any suitable dosage in the method of the present invention. In some embodiments, mifepristone can be administered at a dosage of about 100 mg to about 2000 mg. In other embodiments, dosages of 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, or 2000 mg can be used. In some embodiments, the dosage is of from about 300 to about 1600 mg mifepristone. In some embodiments, the dosage is of from about 300 to about 900 mg mifepristone. In some embodiments, the dosage is of from about 500 to 700 mg mifepristone. In some embodiments, the dosage is of from about 900 to about 1500 mg mifepristone. In some embodiments, the dosage is of from about 1100 to about 1300 mg mifepristone. In some embodiments, the dosage is of from about 500 to about 1500 mg mifepristone. In some embodiments, the dosage is of from about 400 to about 800 mg mifepristone. In some embodiments, the dosage is of about 600 mg mifepristone. In some embodiments, the dosage is of from about 1000 to about 1400 mg mifepristone. In some embodiments, the dosage is of about 1200 mg mifepristone. The dosages, however, can be varied depending upon the requirements of the patient and the condition being treated. The dose administered to a patient, in the context of the present invention, should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the practitioner.

The mifepristone can be administered by any suitable means. Formulations of the present invention include mifepristone in combination with pharmaceutical excipients. Mifepristone is commercially available from a variety of sources such as Eurolabs Ltd. (London, England). Mifepristone can also be synthesized by one of skill in the art using

known synthetic procedures. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co, Easton Pa. ("Remington's").

Oral dosage forms can consist of formulations including (a) liquid solutions, such as an effective amount of mifepristone suspended in diluents, such as water, saline or PEG 400; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, microcrystalline cellulose, gelatin, colloidal silicon dioxide, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, e.g., sucrose, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like containing, in addition to the active ingredient, carriers known in the art.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The composition can, if desired, also contain other compatible therapeutic agents. Preferred pharmaceutical preparations can deliver the compounds of the invention in a sustained release formulation.

Single or multiple doses of mifepristone formulations can be administered depending on the dosage and frequency as required and tolerated by the patient. Mifepristone can be administered for any period of time, such as at least 1 day. In further embodiments, mifepristone can be administered for 2, 3, 4, 5, or 6 days. In certain embodiments of the invention, mifepristone is administered daily for at least 7 days. Mifepristone can also be administered using more daily doses over a longer period of time, such as via 28 daily doses over a period of 28 days. Longer times for administration of mifepristone are also within the scope of the present invention.

Oral bioavailability refers to the fraction of mifepristone absorbed by a subject upon mifepristone administration via a method of the present invention. Bioavailability is reflected in the observed "exposure" which is measured as the integral of a plot of mifepristone concentration in plasma vs. time during or after administration. This integral is referred to as the "area under the curve" or AUC. As used herein, "exposure" in synonymous with "AUC." In some embodiments of the invention, absolute bioavailability can be assessed by comparing the AUC resulting from the method of the invention with the AUC resulting from intravenous mifepristone administration. In certain embodiments of the invention, relative bioavailability can be assessed by comparing the AUC resulting from the method of the invention with the AUC resulting from mifepristone administration via an alternative route. The term "$C_{max}$" refers to the maximum observed plasma concentration of mifepristone resulting from administration via a method of the present invention or via an alternative route.

The method of the present invention includes administration of mifepristone within 1 hour of a consuming a meal and is sufficient to increase $C_{max}$ and AUC values as compared to those values resulting from administration of mifepristone without food. $C_{max}$ and AUC can increase by any amount including 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, and 50%. Increases greater than 50% can also occur according to the method of the invention. In some embodiments, the $C_{max}$ increases by at least 5% compared to the administration of mifepristone in the absence of the meal. In some embodiments, the $C_{max}$ increases by at least 15% compared to the administration of mifepristone in the absence of the meal. In some embodiments, the $C_{max}$ increases by at least 15% compared to the administration of mifepristone in the absence of the meal. In some embodiments, the AUC increases by at least 5% compared to the administration of mifepristone in the absence of the meal. In some embodiments, the AUC increases by at least 15% compared to the administration of mifepristone in the absence of the meal. In some embodiments, the AUC increases by at least 25% compared to the administration of mifepristone in the absence of the meal. In some embodiments, the $C_{max}$ increases by at least 5% and the AUC increases by at least 5% compared to the administration of mifepristone in the absence of the meal. In some embodiments, the $C_{max}$ increases by at least 15% and the AUC increases by at least 15% compared to the administration of mifepristone in the absence of the meal. In some embodiments, the $C_{max}$ increases by at least 25% and the AUC increases by at least 25% compared to the administration of mifepristone in the absence of the meal.

The meal can be any suitable meal. Suitable meals can be high fat meals, moderate fat meals, low fat meals, or meals without any fat. Other suitable meals include high calorie meals. A high-fat meal is one where approximately 50 percent of total caloric content of the meal is fat. A high-calorie meal includes approximately 800 to 1000 calories. The meal can have approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. An example test meal includes two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. Another example of a meal includes a moderate fat breakfast (34% of total calories from fat). Other meals useful in the present invention are known to one of skill in the art.

B. Patients in Need

A patient according to the present invention is a subject in need of mifepristone administration. Preferably, the patient is a mammal having a condition known to be treated by glucocorticoid antagonists such as mifepristone. Such conditions include, but are not limited to, psychiatric illnesses and endocrine disorders. Most preferably, the patient is a human. In one embodiment of the present invention, the patient is a male.

Patients amenable to treatment with mifepristone according to the methods of the present invention suffer from conditions including, but not limited to, obesity, diabetes, cardiovascular disease, hypertension, Syndrome X, depression, psychotic major depression, anxiety, psychotic major depression, Cushing's syndrome, glaucoma, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), neurodegeneration, Cushings disease, Alzheimer's disease, Parkinson's disease, cognition enhancement, Addison's Disease, osteoporosis, frailty, muscle frailty, inflammatory diseases, osteoarthritis, rheu-

matoid arthritis, asthma and rhinitis, adrenal function-related ailments, viral infection, immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, multi-drug resistance, addiction, psychosis, anorexia, cachexia, post-traumatic stress syndrome, post-surgical bone fracture, medical catabolism, mild cognitive impairment, psychosis, dementia, hyperglycemia, stress disorders, antipsychotic induced weight gain, delirium, cognitive impairment in depressed patients, cognitive deterioration in individuals with Down's syndrome, psychosis associated with interferon-alpha therapy, chronic pain, pain associated with gastroesophageal reflux disease, postpartum psychosis, postpartum depression, neurological disorders in premature infants, and migraine headaches.

In some embodiments, the patient suffers from a mental or neurological disorder or condition such as depression, psychotic major depression, anxiety, neurodegeneration, Parkinson's disease, Alzheimer's disease, compulsive behavior, addiction, psychosis, anorexia, cachexia, post-traumatic stress syndrome, cognition enhancement, mild cognitive impairment, psychosis, dementia, delirium, cognitive impairment in depressed patients, cognitive deterioration in individuals with Down's syndrome, psychosis associated with interferon-alpha therapy, postpartum psychosis, postpartum depression, or neurological disorders in premature infants.

In other embodiments, the patient suffers from a metabolic or cardiovascular disorder or condition such as obesity, diabetes, hyperglycemia, antipsychotic induced weight gain, cardiovascular disease, or hypertension.

In some embodiments, the patient suffers from a viral or immune disorder or condition such as viral infection, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), immunodeficiency, immunomodulation, or autoimmune diseases.

In some embodiments, the patient suffers from a bone or inflammatory disorder or condition such as post-surgical bone fracture, osteoporosis, frailty, muscle frailty, inflammatory diseases, asthma and rhinitis, osteoarthritis, or rheumatoid arthritis.

In some embodiments, the patient suffers from a disease or condition such as Syndrome X, Addison's Disease, adrenal function-related ailments, glaucoma, allergies, wound healing, multi-drug resistance, medical catabolism, stress disorders, chronic pain, pain associated with gastroesophageal reflux disease, or migraine headaches.

The term "psychotic major depression," also referred to as "psychotic depression" (Schatzberg (1992) *Am. J. Psychiatry* 149:733-745), "psychotic (delusional) depression" (Ibid.), "delusional depression" (Glassman (1981) supra) and, "major depression with psychotic features" (see the DSM-III-R), refers to a distinct psychiatric disorder which includes both depressive and psychotic features. Individuals manifesting both depression and psychosis, i.e. psychotic depression, are herein referred to as "psychotic depressives." It has been long-recognized in the art as a distinct syndrome, as described, for example, by Schatzberg (1992) supra. Illustrative of this distinctness are studies which have found significant differences between patients with psychotic and nonpsychotic depression in glucocorticoid activity, dopamine-beta-hydroxylase activity, levels of dopamine and serotonin metabolites, sleep measures and ventricle to brain ratios. Psychotic depressives respond very differently to treatment compared to individuals with other forms of depression, such as "non-psychotic major depression." Psychotic depressives have a low placebo response rate and respond poorly to antidepressant therapy alone (without concurrent antipsychotic treatment). Psychotic depressives are markedly unresponsive to tricyclic (anti-depressive) drug therapy (Glassman, et al. (1975) supra). While psychotic depressives can respond to electroconvulsive therapy (ECT), their response time is relatively slow and the ECT has a high level of related morbidity. Clinical manifestations and diagnostic parameters of "psychotic major depression" is described in detail in the DSM-IV (Kaplan, ed. (1995) supra). Thus, due to its unique pathophysiology, high rate of morbidity and response to treatment, there is great practical need to differentially diagnose and specifically treat psychotic major depression as compared to non-psychotic depression.

In some embodiments, the present invention provides a method for improving absorption of mifepristone in a patient suffering from psychotic major depression. The method includes the administration of a dose of from about 100 mg to about 2000 mg mifepristone to the patient within 1 hour after consuming a meal, such that the pharmacokinetics of mifepristone are altered by increasing the maximum plasma concentration ($C_{max}$) and increasing the area under the curve (AUC) compared to administering mifepristone without food, thereby increasing mifepristone absorption.

Cushing's syndrome is a endocrine disease with an estimated incidence of approximately 10 per 1 million persons (Meier and Biller (1997) *Endocrinol Metab Clin North Am* 26:741-762). Cushing's syndrome is associated with an increased blood concentration of cortisol (hypercortisolism) or the presence in blood of glucocorticoid hormone excess over a long period of time. Cushing's syndrome is classified as either ACTH dependent or non ACTH dependent. ACTH dependent Cushing's syndrome is characterized by a chronic ACTH hypersecretion which stimulates the growth of the adrenal glands and the hypersecretion of corticosteroids. The most common underlying cause of ACTH dependent Cushing's syndrome is excessive production of ACTH by pituitary adenomas known as Cushing's disease. Cushing's syndrome resulting from the production of ACTH in another location than the pituitary gland is known as ectopic Cushing's syndrome. Examples of ectopic sites include thymoma, medullary carcinoma of the thyroid, pheochromocytoma, islet cell tumors of the pancreas and small cell carcinoma of the lung. ACTH independent Cushing's syndromes are caused by adrenal tumors that can be either adenomas or carcinomas. Both adrenal adenomas and carcinomas are characterized by chronic cortisol hypersecretion.

Symptoms of Cushing's syndrome include a characteristic abnormal fat deposition around the neck, thinning of the skin, osteoporosis, moon face, weakness, fatigue, backache, headache, impotence, muscle atrophy, increased thirst, urination, insulin resistance, dyslipidemia, myopathy, amenorrhea, hypertension, weight gain, central obesity, steroid hypersecretion, elevated urinary cortisol excretion and mental status changes, in particular depression (Orth (1995) *N. Engl. J. Med* 332:791-803; Dahia and Grossman (1999) *Endocr. Rev.* 20:136-55).

In some embodiments, the present invention provides a method for improving absorption of mifepristone in a patient suffering from Cushing's syndrome. The method includes the administration of a dose of from about 100 mg to about 2000 mg mifepristone to the patient within 1 hour after consuming a meal, such that the pharmacokinetics of mifepristone are altered by increasing the maximum plasma concentration ($C_{max}$) and increasing the area under the curve (AUC) compared to administering mifepristone without food, thereby increasing mifepristone absorption.

C. Assay for Testing Mifepristone Levels

Mifepristone levels can be determined by any method known in the art. Methods for detecting mifepristone levels include, but are not limited to, radio-immuno assay and mass spectrometry (MALDI, SELDI, LS/MS, LS/MS/MS, among others). Liquid chromatography mass spectrometry (LC/MS or LC-MS) separates compounds chromatographically before they are introduced to the ion source and mass spectrometer. It differs from GC/MS in that the mobile phase is liquid, usually a combination of water and organic solvents, instead of gas. Most commonly, an electrospray ionization source is used in LC/MS.

Tandem mass spectrometry (MS/MS) involves multiple steps of mass selection or analysis, usually separated by some form of fragmentation. A tandem mass spectrometer is one capable of multiple rounds of mass spectrometry. For example, one mass analyzer can isolate one peptide from many entering a mass spectrometer. A second mass analyzer then stabilizes the peptide ions while they collide with a gas, causing them to fragment by collision-induced dissociation (CID). A third mass analyzer then catalogs the fragments produced from the peptides. Tandem MS can also be done in a single mass analyzer over time as in a quadrupole ion trap. There are various methods for fragmenting molecules for tandem MS, including collision-induced dissociation (CID), electron capture dissociation (ECD), electron transfer dissociation (ETD), infrared multiphoton dissociation (IRMPD) and blackbody infrared radiative dissociation (BIRD). One of skill in the art will appreciate that other assays for testing mifepristone levels are known to one of skill in the art.

In some embodiments, the assay can be performed as follows. Blood is collected from a patient in a vacutainer containing sodium heparin. The blood is centrifuged and the resulting plasma frozen at an appropriate temperature until assay. In some embodiments, the temperature is about −70° C. In other embodiments, other blood components can be collected and stored. Prior to analysis, the plasma is thawed and a fraction of the plasma is mixed with an internal standard in a solvent such as acetonitrile, to obtain a fixed concentration of the standard. In some embodiments, the internal standard can be mifepristone-$d_4$. The concentration of the internal standard is selected in order to be greater than the expected concentration of mifepristone in the plasma. For example, the internal standard can have a concentration of 2000 ng/mL. One of skill in the art will appreciate that other internal standards, and other concentrations, are useful in the present invention.

Base is then added to the sample solution. The base can be any amine or ammonium base, such as ammonium hydroxide. One of skill in the art will appreciate that other bases are useful in the present invention.

Solvent is then added to the solution and the mifepristone (along with the internal standard) are extracted from the plasma. Solvents useful for the extraction of mifepristone include, but are not limited to, hexanes, pentanes, ethers (such as diethylether, tetrahydrofuran and methyl-t-butyl ether (MTBE)), ethyl acetate, chloroform and methylene chloride. One of skill in the art will appreciate that other solvents are useful in the present invention.

Following separation and concentration of the organic layer, the sample is reconstituted in a solvent mixture comprising water, acetonitrile and formic acid. The ratio of the solvent components can vary. In some embodiments, the solvent mixture is water:acetonitrile:formic acid (75:25:0.1, v/v/v). One of skill in the art will appreciate that other solvent mixtures are useful in the present invention.

The sample can then be analyzed by reverse-phase high pressure liquid chromatography (HPLC). In some embodiments, the reverse-phase HPLC is performed using a water: acetonitrile:formic acid (60:40:0.1) mobile phase (isocratic) at a flow rate of 0.3 mL/min. One of skill in the art will appreciate that other mobile phases and flow rates are useful in the present invention.

The reverse-phase HPLC column can be a phenyl column maintained at 50° C. Mifepristone elutes at 4.2 minutes. Following elution, the mobile phase can be nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds detected using a tandem quadrupole mass spectrometer. Mifepristone (molecular weight of 430 g/mol) can be detected at m/z 372.30. The internal standard mifepristone-$d_4$ can be detected at m/z 376.30. The ratio of the mifepristone peak height to the peak height for the internal standard can then be calculated.

The plasma concentration of mifepristone is then calculated by comparing the experimental ratio to a standard curve of mifepristone:mifepristone-$d_4$ peak height ratio v. mifepristone concentration. The standard curve is generated by first measuring the mifepristone:mifepristone-$d_4$ peak height ratios for mifepristone samples at 10, 20, 50, 100, 200, 500, 1000 and 2000 ng/mL where the mifepristone-$d_4$ internal standard has a concentration of 2000 ng/mL. The mifepristone:mifepristone-$d_4$ peak height ratios of these known solutions are then fit to a power equation (Mass Lynx by Micromass, Beverly, Mass.), against which future samples with unknown concentrations of mifepristone are compared.

## IV. Examples

### Example 1. Food Effect Studies

Multiple studies evaluated the effect of food on the pharmacokinetics of mifepristone and its metabolites. In all studies, healthy adults were randomized to a sequence of administration of mifepristone drug product under fasting and fed conditions.

Fed Group (50% Fat)

Studies C1073-12 and C1073-20 evaluated the effects of a standardized high-fat (50% fat), high calorie breakfast on the pharmacokinetics of single 600 mg doses of mifepristone tablets and 1200 mg doses of mifepristone, respectively. Study C1073-27 evaluated the pharmacokinetic effects of a typical breakfast (34% fat) administered during 7 days of multiple dose administration (mifepristone 1200 mg/day) followed by a standardized high-fat (50% fat) breakfast on the eighth day. In all three studies, the fed state increased plasma mifepristone $C_{max}$ and exposure in comparison to the fasted state, and the point estimate for the size of the effect was consistently larger for AUC than that for $C_{max}$. In the single dose studies, the increases in $C_{max}$ and exposure with food were both numerically larger for the 1200 mg dose of mifepristone compared to that for the 600 mg dose, suggesting a possible dose-related effect. Multiple dosing of mifepristone at 1200 mg/day for 7 days with typical fat meals showed a mean 65% increase in mifepristone exposure relative to 7 days of administration in the fasted state. Switching to administration with a high fat meal on day 8 after 7 days of administration with typical fat meals had little or no effect on either $C_{max}$ or exposure, indicating that fat content is not a major factor in producing the fed/fasted difference.

Fed Group (34% Fat)

Data have also been obtained on the effect of a moderate fat (34% fat) breakfast on the PK of mifepristone following mifepristone doses of 600 mg/day for 7 days. These data were obtained from cohort 3 of a Phase I clinical pharmacology trial (Study CORT-108297-102).

The test group was comprised of 10 healthy adult subjects who were randomized to receive mifepristone at 600 mg/day for up to 14 days in Cohort 3 of Study CORT-108297-102. For this comparison the PK data after 7 days of dosing were used. Subjects were given a moderate fat breakfast (34% of total calories from fat), which on average contained 27 g protein (13%), 32 g fat (34%), and 111 g carbohydrate (53%), totaling approximately 836 calories. The meal was given every day at approximately 30 min prior to receiving mifepristone, which was dosed as two 300 mg tablets once daily.

Day 7 PK parameters from two historical studies (Studies C-1073-05 and C-1073-300 Part II) were used as the reference group for this analysis. In these studies, a total of 52 healthy adults received 600 mg/day of mifepristone for at least 7 days in the fasted.

Demographics across the test and reference groups were similar for weight, height, and body mass index (BMI), based on mean and median values and the overlap of 95% confidence intervals about the mean. In the fed group, there were 5 Caucasians (50%), 2 Hispanics (20%), and 3 African Americans (30%). In the combined reference group, there were 31 Caucasians (59.6%), 8 Hispanics (15.4%), 4 African Americans (7.7%), 3 Asians (5.8%) and 6 subjects of other ethnicities (11.5%). Thus, Caucasians accounted for approximately half of the subjects in both the fed and fasted groups, with the remaining subjects representing a racially/ethnically diverse population. Gender was mostly male in both groups.

In this food effect study of doses of 600 mg/day for 7 days, Day 7 PK parameters of mifepristone under fed conditions (34% fat breakfast) (CORT-108297-102) were compared to fasting conditions using historical data from Studies C-1073-05 and C-1073-300, Part II. Dosing with mifepristone 600 mg/day for 7 days following a breakfast of 34% fat (a moderate fat meal) yielded increases in mifepristone $C_{max}$ and $AUC_{0-24}$ of 34% and 44%, respectively, as compared to the same dose in the fasted state. Thus, mifepristone plasma $C_{max}$ and AUC are higher when the drug is taken in the fed state as compared to the fasted state.

Mifepristone pharmacokinetics after multiple dosing of mifepristone show strong lack of dose proportionality, with little increase in exposure or $C_{max}$ as dose increases above 600 mg. The effect of food on exposure and $C_{max}$ at doses above 600 mg is considerably larger than that which can be achieved by dose increase alone for mifepristone administered in the fasted state. Results of the 90% confidence interval testing for the 3 food effect studies are provided for mifepristone in Table 1.

TABLE 1

90% Confidence Intervals for Mifepristone PK Parameters in Food Effect Studies and Studies with Food Effect Assessments

| Parameter | Dose | Condition | % Fat | N | Geo Mean | Ratio of Geometric Means | 90% CI | Study |
|---|---|---|---|---|---|---|---|---|
| Cmax | 600 mg | Fast | | 49 | 2306 | 1.19 | 1.06-1.33 | 12 |
| (ng/mL) | single dose | Fed | 50% | 49 | 2735 | | | |
| | 1200 mg | Fast | | 23 | 2828 | 1.30 | 1.24-1.65 | 20 |
| | single dose | Fed | 50% | 22 | 3663 | | | |
| | 1200 mg/ | Fast | | 22 | 3223 | 1.56 | 1.41-1.74 | 27 |
| | day × 7 days | Fed | 34% | 24 | 5039 | | | |
| | 600 mg/ | Fast | | 52 | 3041 | 1.34 | 1.10-1.63 | C3 * |
| | day × 7 days | Fed | 34% | 10 | 4072 | | | |
| AUCinf | 600 mg | Fast | | 49 | 103905 | 1.29 | 1.15-1.45 | 12 |
| (hr * ng/mL) | single dose | Fed | 50% | 49 | 134083 | | | |
| | 1200 mg | Fast | | 22 | 133881 | 1.42 | 1.23-1.65 | 20 |
| | single dose | Fed | 50% | 22 | 190638 | | | |
| AUC0-24 | 1200 mg/ | Fast | | 22 | 44174 | 1.65 | 1.52-1.79 | 27 |
| (hr * ng/mL) | day × 7 days | Fed | 34% | 24 | 72766 | | | |
| | 600 mg/ | Fast | | 52 | 43564 | 1.44 | 1.17-1.76 | C3 * |
| | day × 7 days | Fed | 34% | 10 | 62579 | | | |

* C3 = Cohort 3 from Phase I study CORT-108297-102. Comparison was to combined data in healthy

## Example 2. Treatment of Male Patient with Psychotic Major Depression

A 50 year-old male, weighing 175 pounds, presents to a physician with psychotic major depression (PMD). The physician prescribes 600 mg of mifepristone to be taken daily over a period of seven days within 1 hour of eating a normal breakfast.

## Example 3. Treatment of Male Patient with Cushing's Syndrome

A 50 year-old male, weighing 175 pounds, presents to a physician with Cushing's syndrome. The physician prescribes 600 mg of mifepristone to be taken daily over a period of seven days within 1 hour of eating a normal breakfast.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

What is claimed is:

**1**. A method of improving absorption of mifepristone in a patient suffering from Cushing's Syndrome, comprising

administering to the patient for at least 7 days an oral dose of mifepristone of 1200 mg per day within 30 minutes after consuming a meal, such that the pharmacokinetics of mifepristone are altered by increasing the maximum plasma concentration (Cmax) and increasing the area under the curve (AUC) as compared to the Cmax and AUC that would result from administering mifepristone without food in the fasted state in the absence of the meal, said increase in AUC being at least 44% and thereby increasing mifepristone absorption in the patient.

**2**. The method of claim **1**, wherein the patient is a male.

**3**. The method of claim **1**, wherein the mifepristone is administered as a single dose.

**4**. The method of claim **1** where the patient suffers from Cushing's disease.

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